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Awareness with recall during general anesthesia

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Academic Dissertation

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Contents

Abstract

Awareness with recall is a rare but serious complication of general anesthesia with potentially very disabling psychiatric consequences. Prerequisites for the phenomenon of awareness and recall are (1) consciousness with the ability to receive and process sensory information, (2) storage of the processed information in memory, and (3) recollection of the stored information at some later time.

The present study examines incidence of awareness with recall during general anesthesia, the effects of anesthetic agents on it, methods of detecting and preventing it, and its psychiatric and medico-legal after-effects. A total of 3,868 cases (1,485 male and 2,383 female) were included in this study. Structured interviews were conducted after general anesthesia for cardiac or general surgery to find patients who had experienced awareness during anesthesia and were able later to recall their experience. Additional cases were identified from insurance claims based on awareness with recall filed with the Patient Insurance Association in Finland. Psychiatric interview and testing were used to evaluate after-effects of awareness and recall. Feedback information was given to cardiac anesthesiologists in order to study the possibility of reducing incidence of awareness with recall by educational means. Artificial neural networks were used to evaluate the likelihood of detecting intraoperative awareness on the basis of conventional monitoring information.

In the present studies, the incidence of undisputed intraoperative awareness was 0.2-0.4 % of all general anesthetics given for general surgery procedures, while the incidence was about 0.3 % during cardiac anesthesia. Both incidences are 6 to 7 fold higher if cases of possible awareness and recall are included. Lower doses of primary anesthetic agents were given to patients with awareness and recall when compared to controls (isoflurane 0.42 Fi% vs. 0.65 Fi% [$p<0.005$] and propofol 73 µg/kg/min vs. 228 µg/kg/min [$p<0.05$], during general surgery respectively; midazolam 0.8 µg/kg/min vs. 1.1 µg/kg/min [$p<0.05$] during cardiac surgery respectively). Standard physiologic monitoring used during general anesthesia did not reliably detect inadequate depth of anesthesia, even when analyzed with computer-based artificial intelligence. Information given to anesthesiologists about intraoperative awareness lead to a decreasing trend in its incidence with simultaneous increase in the use of anesthetics and decrease in the use of muscle relaxants.

The psychiatric studies revealed anxiety in one patient after awareness and recall. In addition, a case of pre-existing depression was exacerbated after an episode of awareness and recall. Awareness during general anesthesia has triggered a small number of Patient Insurance claims in Finland (about 1 % of anesthesia-related claims). Seventy percent of the patients who filed insurance claims received compen-

sations for pain; the average amount of compensation was EUR 1,000.

Awareness with recall is a rare complication of general anesthesia and its incidence is on the decline. Insufficient dosing of general anesthetics contributes significantly to the present incidence and it is likely that informing anesthesiologists about this complication would decrease it further Awareness cannot be detected by standard monitoring; better monitoring tools need to be developed. The incidence of psychiatric after-effects of intraoperative awareness is not known. In Finland, a small number of Patient Insurance claims has been the only medico-legal after-effect of this complication.

List of original publications

1. Ranta S., Laurila R., Saario J., Ali-Melkkilä T., Hynynen M.: Awareness with recall during general anesthesia - Incidence and risk factors. *Anesth Analg* 86: 1084-1089, 1998.

2. Ranta S., Jussila J., Hynynen M.: Recall of awareness during cardiac anaesthesia: influence of feedback information to the anaesthesiologist. *Acta Anaesthesiol Scand* 40:554-560, 1996.

3. Ranta S., Herranen P, Hynynen M.: Patients' conscious recollections from cardiac anesthesia. *J Cardiothorac Vasc Anesth* 16:426-430, 2002.

4. Ranta S., Hynynen M., Räsänen J: Application of artificial neural networks as an indicator of awareness with recall during general anaesthesia. *J Clin Monit Comput* 17:53-60, 2002.

5. Ranta S., Ranta V., Aromaa U.: The claims of compensation for awareness with recall during general anaesthesia in Finland. *Acta Anaesthesiol Scand* 41:356-359, 1997.

Abbreviations

AA	Anesthetic agent
AEP	Auditory evoked potential
AER	Auditory evoked response
ANOVA	Analysis of variance
ASA	American Society of Anesthesiologists
BIS	Bispectral index
BP	Blood pressure
CABG	Coronary artery bypass grafting
CI	Confidence interval
CO_2	Carbon dioxide
D&C	Dilatation and curettage
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
EBT	Endobronchial tube
EC_{50}	Effective concentration in 50 percent of the subjects
ECG	Electrocardiogram
EEG	Electroencephalogram
ET	End-tidal
ETAGC	End-tidal anesthetic gas concentration
ETT	Endotracheal tube
EUR	Euro
Fi	Inspiratory fraction
FIM	Finnish Mark
GBP	Pound sterling
i.v.	Intravenous
ICU	Intensive care unit
IFT	Isolated forearm technique
MAC	Minimum alveolar concentration
MLAEP	Mid-latency auditory evoked potential
MVR	Mitral valve replacement
N.A.	Not assessed
N_2O	Nitrous oxide
NMB	Neuro-muscular blocker
ns.	non-significant
PACU	Post-anesthesia care unit
PIA	Patient Insurance Association
P_k	Prediction probability
PTSD	Post-traumatic stress disorder
SaO_2	Arterial blood oxygen saturation
SE	Standard error
Tx	Transplantation
USD	United States Dollar

1. Introduction

Conscious awareness with recall as a complication of general anesthesia has existed for as long as general anesthesia itself. In 1846, William Morton gave the first anesthetic to Gilbert Abbott in a demonstration at the Massachusetts General Hospital in Boston. Gilbert Abbott told later that he was aware during the anesthetic but felt no pain. Only a small number of further reports of awareness during anesthesia were published in the nineteenth and in the early twentieth century (Ghoneim, 2001). In the early days of anesthesia, the practice of using a single general anesthetic agent in relatively high concentrations to produce all components of general anesthesia – unconsciousness, relief from pain, absence of reflexes, and muscle relaxation – apparently protected the patients from traumatic awareness. Moreover, neuromuscular blocking agents (NMB) were not available, and patients were, therefore, able to signal awareness by movement. When NMBs were introduced into anesthetic practice to improve operative conditions and to reduce the toxicity of general anesthetic agents, traumatic awareness became possible.

The first case report of traumatic conscious awareness with later recall during general anesthesia was described in 1950 (Winterbottom, 1950). Perhaps describing the attitude of some members of the medical profession towards this complication, the surgeon who operated on the patient reported by Winterbottom, later published a letter where he wrote that "the anaesthetic as a whole could only be described as excellent" (Wells, 1950). Studies of the incidence of awareness with recall began in the 1960s. Generally, the possible traumatic psychologic sequelae of this complication were not acknowledged in the medical literature until the 1970s. However, despite several decades of attention to this problem, patient groups and, especially, individual patients at risk have not been clearly identified, the definition of this complication is not entirely clear, its prevention has not been studied in detail, and the nature and incidence of possible after-effects of awareness during general anesthesia are not known. Furthermore, this complication is one of the most frequent fears of our patients. In a preoperative interview study, 54 % of patients were anxious about not being asleep during the operation (McCleane, and Cooper, 1990).

This thesis focuses solely on awareness with explicit recall during general anesthesia. The possibility of subconscious learning and memory during general anesthesia, or its possible sequelae are not discussed.

2. Review of the literature

2.1. Definitions

2.1.1. General anesthesia

General anesthesia is a state characterized by unconsciousness, analgesia, muscle relaxation, and depression of reflexes (Willenkin, 1990) or, the administration of chemical agents to produce reversible unconsciousness and depression of reflex response to afferent stimuli (Critchley, 1978). However, there are also definitions of anesthesia where loss of consciousness, an all-or-none phenomenon, defines the beginning and ending of the anesthetic state (Prys-Roberts, 1987). Thus, analgesia, muscle relaxation, and suppression of autonomic activity, are not components of anesthesia, but rather, should be considered as desirable supplements to the state of anesthesia (Prys-Roberts, 1987). Other authors, however, consider that the state of general anesthesia includes different, smoothly changing states of consciousness (Jones, and Konieczko, 1986). As the present thesis focuses on awareness during general anesthesia with explicit recall occurring afterwards, the term 'unconsciousness' becomes the most important component of general anesthesia. It should be clear that by preventing consciousness during general anesthesia there should be no recall of it.

2.1.2. Consciousness

The term 'consciousness' is explained as "the state of being conscious; awareness of one's own existence, sensations, thoughts, surroundings, etc." (Anonymous, 1989). Consciousness involves four functions: stimulus uptake (perception), stimulus processing (mnemonic representation), stimulus evaluation (emotion), and stimulus response (volition). These processes are integrated by complex neuronal systems to achieve regional linking within one modality, temporal, and semantic binding of information. (Pöppel, and Schwender, 1993).

2.1.3. Awareness

The term 'awareness' is explained as "having knowledge, conscious, cognizant" (Anonymous, 1989). The term represents the state of mind at a certain moment of time irrespective of whether that state is later recalled or not (Ghoneim, and Mewaldt, 1990). However, Jones and Konieczko have claimed, that there would be different stages of "conscious awareness" and that also "unconscious awareness" would be possible (Jones, and Konieczko, 1986).

In medical terminology, the term "awareness" has sometimes been regarded as meaning only consciousness during general anesthesia (Critchley, 1978). This usage is different from both the general meaning of the term and its meaning in the context of psychological research. Therefore, the ‘medicalization’ of the term “awareness” is best avoided.

In this thesis, the terms “awareness” and “consciousness” are used interchangeably, as suggested by Ghoneim and Block (Ghoneim, and Block, 1997). As general anesthesia is defined as a state of unconsciousness, it would logically follow that a patient under general anesthesia cannot be aware, and the converse. The term “awareness during general anesthesia” is, however, almost universally accepted by both medical and legal circles, and its meaning is well understood. Therefore, this term is used in this thesis, and in other papers, as there is no simple substitute (Payne, 1994).

2.1.4. Memory and Recall

Memory is essential for the recall of intraoperative perception. As a cognitive function, memory has been divided to a variety of subsystems (Andrade, and Baddeley, 1993). These include a working memory comprising a ‘phonological loop’ for linguistic memory and ‘visuospatial sketchpad’ for visual and spatial information processing, and a ‘central executive’ which organizes the process. The processed ideas are then transferred from working memory to long term memory for storage, and possible retrieval. Forgetting is possible in both the working memory and long term memory. Responding to ideas retrieved from long term memory requires that these ideas are processed again in the working memory. (Baddeley, 1990; Andrade, and Baddeley, 1993; Bailey, and Jones, 1997)

The anatomical representation of the working memory in the human brain is the prefrontal cortex. The long term memory is scattered in the medial temporal lobe, the hippocampus, and the posterior neocortex (Bailey, and Jones, 1997).

The retrieval from memory can be either a conscious or subconscious process. The former, explicit memory retrieval, includes the spatio-temporal context in which the recalled event occurred, and the latter, implicit memory retrieval, is revealed by a change in task performance (Kihlstrom, and Schacter, 1990). Explicit memory is also called declarative and implicit memory non-declarative (Bailey, and Jones, 1997). Declarative memory is further divided into episodic, or autobiographical memory, and semantic, or factual memory (Bailey, and Jones, 1997). Explicit memory requires effortful recall (Bailey, and Jones, 1997). Examples of explicit memory are remembering meeting a person, or recalling having seen an accident. Examples of implicit memory are subconscious processes like walking, or riding a bicycle. It is likely that the learning mechanisms involved in implicit and explicit memory are different (Griffiths, and Jones, 1990).

Memory is tested with direct and indirect tests; the former are used to test explicit recall, the latter test implicit recall. In direct memory tests the subject is asked whether he or she remembers the stimulus such as hearing a word. Of primary importance is not, which words the subject knows but, rather, the specific process of hearing a word in a certain situation. Indirect tests assess the change in the performance of the subject. For example, prior exposure to a certain word increases the likelihood of that word being chosen from a list of words. (Ghoneim, and Block, 1992; Andrade, and Baddeley, 1993)

2.1.5. Awareness with recall during general anesthesia

The experience of awareness with recall during general anesthesia requires general anesthesia and awareness being present in the patient simultaneously. Furthermore, it is required that the patient later recalls this incident.

It is claimed that anesthetic agents prevent the occurrence of awareness with recall by three mechanisms: 1. by interfering with the development of neuronal adequacy for signal processing, 2. by interfering with the establishment of the time marker for the sensory experience thus distorting the experience, and 3. by interfering with recall of the conscious experience (Jessop, and Jones, 1991).

We rely on memory for evidence of what has been perceived during general anesthesia. This evidence, when negative, will always be somewhat equivocal (Kihlstrom, and Schacter, 1990). Accordingly, it is not unequivocally possible to discriminate between patients who have or have not been 'aware' or 'conscious' during general anesthesia. The term 'wakefulness' has been used to describe patients who are able to react meaningfully to stimuli during general anesthesia but are not able to recall either the stimuli or their reactions postoperatively (Tunstall, 1977). There is evidence that a large number of such patients exist (Tunstall, 1977, 1979; Russell, 1985, 1986, 1993; Russell, and Wang, 1997). There also is some evidence that wakefulness without explicit recall might be detrimental for the patient (Wang, 2001) but this has not been definitely proven (Ghoneim, and Block, 1997).

In the present thesis, only awareness with explicit recall is studied. This means that, in a post-operative interview, the patient can recall having had perceptions of some kind during the time-context of general anesthesia. This is called 'awareness with recall' or, for brevity, 'awareness' in this study.

2.2. The nature of the experience of awareness during general anesthesia

The primary characteristics of awareness vary between published reports. In a study of 26 patients with intraoperative awareness based on voluntary referral by anesthesiologists Moerman *et al.* (1993) found that the most common form of recall was hearing sounds, reported by 89 % of the patients. Paralysis was the second most common feeling, recalled by 85 % of the study population, while pain was reported by 39 % of those included in the study

Cobcroft, and Forsdick (1993) recruited patients by advertising in popular magazines, and found pain to be the most common recollection reported by 39 % of those responding to the survey. Recollection of sounds was reported by 31 % of this study population.

Schwender *et al.*, (1998) recruited patients both with advertisements in newspapers and on the internet, and by referral from colleagues. They confirmed auditory perceptions to be the most common sensory modality during intraoperative awareness (100 % of patients). The next most common were tactile perceptions (64 %), and paralysis (60 %); 24 % of the patients felt pain. In a closed claims analysis, auditory perception was recalled by 30 % of the study population, tactile perceptions by 25 %, pain by 21 %, and paralysis by 20 % of the patients (Domino *et al.*, 1999).

2.3. Methods of detecting awareness during general anesthesia

Obviously, detection of learning and explicit memory during general anesthesia, requires interviewing the patient postoperatively (Kihlstrom, and Schacter, 1990; Ghoneim, and Block, 1992). In principal, either a postoperative interview for intraoperative events, or recall or recognition of stimuli presented during anesthesia can be used (Ghoneim, and Block, 1992). Both types require conscious recollection of specific learning episodes (Wolters, and Phaf, 1990).

The postoperative interview should be structured (Ghoneim, and Block, 1992), otherwise a lower incidence of awareness and recall is likely to be found (Jelicic, and Bonke, 1989). A structured interview presents a standard set of questions to all interviewed subjects. Brice *et al.* (1970) have designed five

Table 1. Questions asked during the interviews.

1.	What is the last thing you remember before going to sleep for the operation?
2.	What is the first thing you remember after waking after the operation?
3.	Do you remember anything in between?
4.	Did you have any dreams?
5.	What was the most unpleasant thing you remember from your operation and anesthesia?

simple questions for detecting explicit awareness in a postoperative interview (Table 1).

Some authors, however, have used simpler sets of questions (Lyons, and Macdonald, 1991; Sandin, and Nordström, 1993), and a postoperative interview under hypnosis has been used by others (Goldmann *et al.*, 1987). The value of hypnosis as a tool for studying awareness, learning, or memory during general anesthesia has, however, been questioned (Ghoneim, and Block, 1992).

Typical positive responses indicating awareness are factual memories of discussions, noises, tactile sensations, or episodes of pain or distress that can be traced back to the intraoperative period. Feeling of muscle paralysis has also been considered typical of intraoperative awareness (Bailey, and Jones, 1997). Dreams that are either associated with anesthesia or are altered states of awareness characterized by vivid thoughts and images are considered to be due to inadequate depth of anesthesia (Ghoneim, and Block, 1992).

The timing of the interview has raised much discussion. There is evidence that assessment of learning during anesthesia is more successful later rather than sooner after exposure to inhalational agents (Bennett, 1986). However, there are case reports of patients who remembered an experience of awareness in an early interview but not any more in a later interview (Brice *et al.*, 1970; Harris *et al.*, 1971; Dutton *et al.*, 1995). In a well-conducted study, there was no correlation between general memory performance of intraoperative events and the time-interval between surgery and memory test (Lubke *et al.*, 1999). Recently, it has been shown by Sandin and co-workers that more than one interview over a time period of at least two weeks increases the number of detected cases of awareness (Sandin *et al.*, 2000).

It was noted very early that, in the interviews, it is difficult to know what, if anything, is actually being remembered (Parkhouse, 1960). Some authors have called for better scrutiny of the reported cases by psychiatric interview and hypnosis (Aldrete, and Wright, 1985). The reporting of the recollections of the study patients varies between studies.

There are many ways of studying the implicit memory by indirect testing. These are reviewed, e.g., by Ghoneim, and Block (1992); Bailey, and Jones (1997); and Ghoneim, and Block (1997).

2.4. Incidence of awareness and recall during general anesthesia

2.4.1. General surgery

A large number of studies on the incidence of intraoperative awareness and recall have been published since Winterbottom's original report of this intraoperative complication in 1950 (Winterbottom, 1950). The published studies using postoperative structured interview method are summarized in Table 2

Pedersen, and Johansen (1989) found and incidence of 0.1 % for intraoperative awareness in a study of 7,306 anesthetics conducted without structured interviews. Myles *et al.* (2000) used interviews, although not necessarily structured ones, in another large study, and identified 12 patients with awareness from a group of 10,811 interviewed patients, giving an incidence of awareness of 0.11 %.

In general, the incidence has been on the

Table 2. Incidence of awareness and recall during anesthesia for general surgery. A structured interview method was used in these studies, and patients had undergone general surgical procedures. Gynecological, but not obstetrical, procedures are considered general surgical procedures in this context. Studies on outpatient anesthesia are included.

Reference	*Number of patients*	*Number of interviews, (time of the interviews [h] after anesthesia[1)])*	*Incidence of explicit awareness (%)* [2)]	*Anesthetics used* [3)]
Hutchinson (1960)	656	1 (1st post-operative day)	1.2 (1.4), pain: 63	*P:* [5)] *I:* thp[4)5)] *M:* hal[4)5)], N2O *R:* [5)]
Terrell *et al.* (1969)	37	1 (24-168), including hypnosis	0	*P:* bar[4)5)], mor, sco[4)] *I:* bar[4)5)] *M:* ee[4)], hal[4)], mxf[4)], N2O[4)] *R:* suc[4)], dtc[4)]
Brice *et al.* (1970)	60	3 (i, 24-48, 168-192)	1.7, pain: 100	*I:* thp *M:* N2O *R:* dtc
Harris *et al.* (1971)	120	2 (i, 24-48)	0.8, (1.7), pain: 0	*P:* mor[4)] *I:* thp *M:* N2O, hal[4)] *R:* dtc
Browne, and Catton (1973a)	120	1 (< 48)	1.7, pain: ?	*P:* mep[4)], pmz[4)] *I:* fen, dro, thp *M:* fen, dro, N2O *R:* dtc[4)], pan[4)]
Browne, and Catton (1973b)	112	1 (< 48)	1.8, (2.7), pain: 0	*P:* mep, pmz *I:* thp, fen[4)], dro[4)] *M:* N2O, dro[4)] *R:* dtc[4)], pan[4)]
Wilson *et al.* (1975)	490	2 (24, 48-72)	0.6, (0.8), pain: 0	*P:* used in 98 %[5)] *I:* thp[4)] *M:* N2O, hal[4)], enf[4)], dro[4)], fen[4)], ket[4)] *R:* used[4),5)]
Agarwal, and Sikh (1977)	138	2 (i, 4-8)	0	*P:* dia[4)], mep[4)] *I:* thp *M:* N2O *R:* suc, dtc
Desiderio, and Thorne (1990)	11	2 (i, 1st post-operative day)	0	*P:* mid *I:* alf, mid *M:* alf, mid *R:* vec

Table 2. Continued.

Reference	*Number of patients*	*Number of interviews, (time of the interviews [h] after anesthesia[1)])*	*Incidence of explicit awareness (%)* [2)]	*Anesthetics used* [3)]
Liu *et al.* (1991)	1,000	1 (20-35)	0.2	*P:* bzd[4)5)], sco[4)], antiemetic[4)5)], other sedatives[4)5)], o[4)5)] *I:* ? *M:* ? *R:* suc[4)]
Sandin, and Nordström (1993)	2,500[6)]	1 (i), 2 for the last 1727 patients (i, on leaving PACU[7)])	0.2, pain: 40	*P:* dix, kbe *I:* alf, pro *M:* alf, pro *R:* vec
Miller *et al.* (1996)	90	1 (24-48)	6.7	*P:* - *I:* alf, pro, mid[4)] *M:* alf, pro *R:* atr
Nordström *et al.* (1997)	1,000	3 (i, 12-81, 72-1,392)[8)]	0.2, (0.3), pain: 50	*P:* dix[4)], mid[4)], o[4)5)] *I:* alf, pro *M:* alf, pro *R:* used in all patients[5)]
Sandin *et al.* (2000)	11,785	3 (i, 24-36, 168-336)	Definite: 0.05, Probable: 0.06, Possible: 0.03. Awake paralysis: one case. All: 0.16 Pain reported by 37 % of all cases of awareness	P: o (97.1 %), bzd (17.7. %) *I:* pro (54.9 %), thp (44.5 %), sev (0.31 %), ket (0.24 %) *M:* N2O (93.6 %), sev (66.7 %), iso (33.3 %), pro (2.8 %) *R:* suc (8.7 %), ndr[5)] (65.8 %)

[1)] i = immediately after emergence from the anesthesia

[2)] Incidence of clear awareness is given first, incidence of clear *and* doubtful awareness is given second (in parenthesis) if that can be estimated by the data given in the publication, and incidence of painful awareness (as a percentage of the total cases of *clear* awareness) is given third.

[3)] Abbreviations of anesthetics used:

P = Premedication, *I* = Induction, *M* = Maintenance, *R* = Muscle relaxation,

alf = alfentanil, atr = atracurium, bar = barbiturate, bzd = benzodiazepine, dia = diazepam, dix = dixyrazine, dro=droperidol, dtc = d-tubocurarine, ee = ethyl ether, enf = enflurane, fen = fentanyl, hal = halothane, iso = isoflurane, ket = ketamine, kbe = ketobemidone, mep = meperidine, mhx = methohexital, mid = midazolam, mor = morphine, mxf = methoxyflurane, ndr = non-depolarizing muscle relaxant, N_2O = nitrous oxide, o = opioid; pan = pancurone, pro = propofol, pmz = promethazine,

Table 2. Continued.

sco = scopolamine, sev = sevoflurane, suc = succinylcholine, thp = thiopental, vec = vecuronium

[4] An anesthetic received by some of the patients in the study.

[5] Exact drug(s) not given in the published data.

[6] Numbers are approximate.

[7] PACU = Post anesthesia care unit.

[8] Third interview was accomplished with a questionnaire, and 500 patients anesthetized last in the study series were included.

decline in recent decades (Liu *et al.*, 1991; Moerman *et al.*, 1995; Table 2) but the vast majority of studies continue to report a measurable incidence of this complication. The decline of incidence has been explained by the tendency to use progressively deeper levels of anesthesia (Cormack, 1993). A higher incidence is often cited to be associated with certain types of procedures, especially cardiac surgery, obstetrics, and trauma surgery (Ghoneim, and Block, 1992; Ghoneim, and Block, 1997). The incidence of explicit intraoperative awareness during different types of procedures is reviewed below.

Another source reflecting the frequency of awareness during general anesthesia, are the complication databases. In the Australian Incident Monitoring Study of 2,000 reported complications, awareness during anesthesia was the reason for reporting in 16 cases (0.8 %) (Osborne *et al.*, 1993). In a study using the closed claims database from the U.S.A., claims concerning awareness during general anesthesia resulted in 79 of the 4,183 claims (1.9%) (Domino *et al.*, 1999).

2.4.2. Cardiac surgery

There are several studies on the incidence of awareness and recall during cardiac anesthesia. The incidence figures are given in Table 3. One has to note, that in one study interviews during hypnosis were used (Goldmann *et al.*, 1987). Therefore, the results of that study are not directly comparable with other studies, which have used standard post-operative interview methods.

2.4.3. Other types of surgery

The studies on the incidence of awareness with recall during operative obstetrics are summarized in Table 4.

The study by Crawford is one of the very few studies with a reasonable number of patients comparing different anesthetic protocols in relation to awareness and recall (Crawford, 1988). The incidence of awareness and recall during elective caesarean section was 3.7 % in a group receiving thiopental induction and maintenance of anesthesia with 67 % nitrous oxide (N_2O). In a group that received similar anesthesia with the addition of 0.1 % methoxyflurane after the delivery, the incidence of awareness was 0 %, $p<0.045$. Similarly, in the group of all operative obstetric cases (elective and emergency section plus vaginal deliveries) the incidence of awareness was 3.1 vs. 0.3, $p<0.003$.

An incidence of awareness and recall during caesarean section of 2.8 % has been reported in a study group of 777 patients (Crawford *et al.*, 1985) However, a structured interview method was probably not used in this study.

In the most recent large study, the incidence of awareness with recall during cesarean section during the years 1982 through 1989 was followed. The mean incidence of awareness and recall among the 3.076 patients was 0.9 %. Until and including 1985, the incidence of awareness and recall was 1.3 % and it decreased to 0.4 % thereafter. The anesthetic protocol was changed during 1986: The induction dose of thiopental was increased from

Table 3. Incidence of awareness and recall during cardiac anesthesia.

Reference	*Number of patients*	*Number of interviews, (time of the interviews [h] after anesthesia)*	*Incidence of explicit awareness (%)* [1)]	*Anesthetics used* [2)]
Maunuksela (1977)	139	1 (1st post-operative week)	5.8	*P:* anh+bar *I:* dro[3)], fen[3)], hal[3)], N2O[3)], thp[3)] *M:* dro[3)], hal[3)], N2O[3)] *R:* pan
Kim (1978)	56	1 (24-71)	3.6, (8.9), pain: 50	*P:* hxz, scb *I:* dro, fen, thp *M:* fen[3)], thp[3)], N2O[3)], hal[3)] *R:* pan
Goldman *et al.* (1987)	30	1 (168-240)	6.7, (23.3 [4)]), pain: 0	*P:* pap[3)], sco[3)], lor[3)] *I:* fen[3)], hal[3)], N2O[3)] *M:* fen[3)], hal[3)], N2O[3)] *R:* ?
Phillips *et al.* (1993)	700	1 (96-120)	0.6, (1.1), pain: 50	*P:* ? *I:* dia or mid, fen, thp[3)] *M:* fen, mid[3)], dia[3)], lor[3)] *R:* pan
Dowd *et al.* (1998)	608	1 (18 hours after extubation)	0.3	*P:* dia[3)], lor[3)], mor[3)] *I:* fen, thp[3)] *M:* before bypass iso, mid. During bypass pro, iso[3)], after bypass pro *R:* pan

[1)] Incidence of clear awareness is given first, incidence of clear *and* doubtful awareness is given second (in parenthesis) if that can be estimated by the data given in the publication, and incidence of painful awareness (as a percentage of the total cases of clear awareness) is given third.

[2)] Abbreviations of anesthetics used:

P = Premedication, *I* = Induction, *M* = Maintenance, *R* = Muscle relaxation,

anh=antihistamine, bar=barbiturate, dia = diazepam, dro=droperidol, fen = fentanyl, hal = halothane, hxz = hydroxyzine, iso = isoflurane, lor = lorazepam, mid = midazolam, mor = morphine, N2O = nitrous oxide, pan = pancurone, pap = papaveretum, pro = propofol, scb = secobarbital, sco = scopolamine, thp = thiopental

[3)] A drug received by some of the patients in the study.

[4)] Interviewed under hypnosis.

5 to 7 mg/kg, the maintenance volatile anesthetic was changed from halothane to isoflurane, and the use of a potent inhaled anesthetic was allowed after the delivery (Lyons, and Macdonald, 1991).

In a study of the incidence of awareness

Table 4. Incidence of awareness and recall during general anesthesia for operative obstetrics. A structured interview method is used in these studies.

Reference	*Number of patients*	*Number of interviews, (time of the interviews [h] after anesthesia 1))*	*Incidence of explicit awareness (%)2)*	*Anesthetics used3)*
Bergström, and Bernstein (1968)	17	1 (i)	11.8, (35.3), pain: 50	*P*: sco4) *I:* N2O, hxz4) *M*: N2O, hxz *R:* suc
Wilson, and Turner (1969)	150	2 (i, < 36 h)	2.0, pain: 675)	*P*: ? *I:* thp4) *M:* N2O
Crawford (1971)	8806)	1 (1st post-operative day)	1.67)	*P*: cdz4), mep4), prz4) *I:* sco, thp *M:* N2O, mep4), mxf4) *R:* suc
Ng, and Gurubatham (1974)	138	1 (1st post-operative day)	2.2, pain: 678)	Not reported
Abouleish, and Taylor (1976)	68	1 (24-36)	1.5, pain: 0	*P*: ? *I:* tia *M:* N2O, dia, mor *R:* dtc, pan, suc
Farnsworth (1978)	80	1 (1st post-operative day)	5.0	*P*: ? *I:* thp *M:* N2O, enf4) *R:* suc, dtc4)
Schultetus *et al.* (1986)	36	2 (i, 1st post-operative day)	8.3, pain: 0	*P*: ? *I:* ket4), thp4) *M*: N2O, fen *R*: suc
Baraka *et al.* (1989)	50	2 (i, 1st post-operative day)	4	*P*: - *I:* ket4), thp4) *M:* hal4), N2O4) *R:* suc
Bogod *et al.* (1990)	74	1 (24)	2.7, (12.29)), pain: 50	*P*: - *I:* thp *M*: enf, N2O *R:* atr4), vec4)

Table 4. Continued.

Reference	*Number of patients*	*Number of interviews, (time of the interviews [h] after anesthesia 1))*	*Incidence of explicit awareness (%)2)*	*Anesthetics used3)*
Lyons, and Macdonald (1991)	3,076	1[10]	0.9[11]	***P:*** ? ***I:*** thp ***M:*** hal[4], iso[4], N2O, pap ***R:*** suc, ndr[12]

1) i = immediately after emergence from the anesthesia

2) Incidence of clear awareness is given first, incidence of clear *and* doubtful awareness is given second (in parenthesis) if that can be estimated from the data, and incidence of painful awareness (as a percentage of the total cases of clear awareness) is given third.

3) Abbreviations of anesthetics used:

P = Premedication, ***I*** = Induction, ***M*** = Maintenance, ***R*** = Muscle relaxation,

alf = alfentanil, atr = atracurium, cdz = chlordiazepoxide, dia = diazepam, dtc = d-tubocurarine, enf = enflurane, fen = fentanyl, hal = halothane, hxz = hexobarbitone, iso = isoflurane, ket = ketamine, mep = meperidine, mor = morphine, mxf = methoxyflurane, ndr = non-depolarizing muscle relaxant, N2O = nitrous oxide, pan = pancurone, pap = papaveretum, prz = promazine, sco = scopolamine, suc = succinylcholine, thp = thiopental, tia = thiamylal, vec = vecuronium

4) A drug received by some of the patients in the study.

5) In addition to three patients classified as having experienced awareness, there were 23 (15.3 %) patients with unpleasant dreams and seven of these patients also experienced intraoperative pain.

6) Includes 218 patients undergoing postpartum sterilization

7) Different incidences of awareness for the two study groups, see text for details.

8) In addition to three patients classified as having experienced awareness, there were nine (6.5 %) patients with unpleasant dreams and seven of these patients also experienced intraoperative pain.

9) Includes patients reported to have “had dreams or heard voices”.

10) Time of postoperative interview not specified.

11) Study reported awareness and recall during eight years (1982-1989). Incidence differed over time, see text for details.

12) Exact drug(s) not given in the published data.

with recall during surgery for major trauma, 51 operated patients were divided into two groups: to those who received anesthetics for the intubation and for maintenance of anesthesia during surgery, and to those who did not receive any anesthetic for the intubation and / or did not receive anesthetics for at least twenty minutes during surgery because of unstable hemodynamic condition or because of unconsciousness on arrival at the emergency room. The incidence of awareness with recall, found in two consecutive structured interviews, was 11 % in the former group, and 43 % in the latter (Bogetz, and Katz, 1984). In a recent study, these findings were not confirmed, but rather, the investigators were not able to find any convincing evidence of explicit memories in a series of 96 trauma patients. These patients were anesthetized according to a standardized protocol consisting of etomidate, fentanyl, and isoflurane (Lubke *et al.*, 1999).

Moerman *et al.* (1995) studied the incidence of awareness with recall during cardioverter defibrillator implantation: the patients received diazepam premedication; induction with etomidate and alfentanil, and maintenance with a propofol infusion; an atracurium infusion was used for muscle relaxation. Two of the 33 (6.1 %) patients recalled the defibrillation shocks delivered during the cardioverter implantation. The authors suggest that awareness was due to extravasation of the anesthetic through a hole in the subclavian vein created for the central lead of the defibrillator.

In a study trying to find out the incidence of awareness and recall during intubation 160 patients were interviewed; three (1.9 %) reported intraoperative awareness. However, only two were able to remember the intubation while the third patient recalled paralysis (McKenna, and Wilton, 1973). In a more recent study, 30 patients were anesthetized with different doses of etomidate (0.2–0.4 mg/kg) and fentanyl. The patients' consciousness was monitored during intubation by the isolated forearm technique (IFT). Positive IFT response was found in 80, 70, and 20 % of the patients receiving 0.2, 0.3, and 0.4 mg/kg etomidate, respectively. One of the patients with positive IFT response recalled awareness in a postoperative interview, giving an incidence of awareness with recall of 3.3 % during intubation in this study (St Pierre *et al.*, 2000).

An incidence of awareness and recall of 4.0 % has been reported in patients anesthetized with thiopental for broncho- or laryngoscopy. (Barr, and Wong, 1973). In another study that investigated awareness during bronchoscopy the incidence of awareness with recall was 6.7 % in a group of 104 patients. The anesthetic consisted of thiopental 0.4-1.9 mg/kg/min, and succinylcholine for relaxation (Moore, and Seymour, 1987).

2.5. Reasons for awareness with recall during general anesthesia

2.5.1. General considerations

The causes of awareness with recall have been estimated from cases reported to the British Medical Defence Union (Hargrove, 1987; Table 5). Cases of faulty anesthetic technique include reliance on N_2O only in maintaining anesthesia, and cases where the anesthesiologist considered light anesthesia justified without apparent reasons. Failure to check apparatus includes cases in which a correctable fault in the anesthetic apparatus caused awareness. The authors considered that if a patient was in danger of dying on the operating table, the use of light anesthesia was justified.

The anesthetic care was defined substandard in 54 % of cases of awareness in a report of closed claims analysis in the United States (Domino *et al.*, 1999).

There are few case reports where tolerance to anesthetic agents has been implemented as a reason for recall (Walder, 1995). In general, these cases form a very small minority of the reported cases of awareness with recall. However, it seems that consumption of alcohol, tobacco, or coffee is associated with increased fentanyl requirement during induction of high-dose fentanyl anesthesia (Stanley, and De Lange, 1984).

The majority of cases of awareness and re-

Table 5. Causes of awareness with recall reported to the British Medical Defence Union between 1982 and 1986 (Hargrove, 1987).

Causes	*Percentage of cases*
Faulty anesthetic technique	70
Failure to check apparatus	20
Genuine apparatus failure	5
Spurious claims	2.5
Justified risks / unknown cause	2.5

call seem to be due to preventable problems in the anesthetic apparatus and administration of anesthesia. A smaller fraction of patients seem to suffer from this complication because of individual differences in pharmacokinetics and pharmacodynamics of anesthetic agents. Important differences are known to exist in the distribution of drugs and in their entry into the effector site. The differences between drug concentration and effect are, however, smaller than differences between drug dose and effect (Scheinin, 1999). As many anesthetic drugs are used in standard doses it is likely that the complication of awareness will continue to exist unless the drug effect can be titrated against a specific monitor of consciousness.

2.5.2. Anesthetics

A very large number of studies have compared the effect of different doses of anesthetic agents on learning and memory.

2.5.2.1. The concepts of minimum alveolar concentration and effective concentration

Movement as a response to a noxious stimulus has been used as a measure of the relative potency of volatile anesthetics. Originally, movement as a response variable was chosen because it is an easily observable, categorical variable, and no other simple and unequivocal response variables existed (Eger, 2002). The minimum alveolar concentration (MAC) is the concentration of a volatile anesthetic necessary to eliminate movement in response to surgical stimulation, usually skin incision, in 50 % of subjects (Eger *et al.*, 1965). MAC values of several anesthetic agents are considered to be additive (Eger, 1989). The MAC concept, however, only relates to movement, a response probably mediated by lower, spinal centers of the central nervous system (Rampil, 1994). A concept of MAC-awake has been proposed to describe the concentration needed to abolish consciousness in 50 % of the subjects (Stoelting *et al.*, 1970). MAC is useful in comparing the potencies of different volatile anesthetics (Jones, 2000), however, MAC is based on population studies, and by definition, 50 % of patients are still conscious at MAC_{awake} value. Furthermore, several individual factors like hypothermia, hypotension, hypercarbia, acidosis, and electrolyte disturbances affect MAC. Usually, the effector site (central nervous system) concentration may be estimated by the end-tidal expiratory gas concentration after a reasonable equilibration period. However, ventilation-perfusion mismatch may cause a variable difference between the end-tidal and arterial blood gas concentration (Quasha *et al.*, 1980). These factors render MAC alone unsuitable for monitoring unconsciousness or depth of anesthesia in an individual patient.

An analogous value for intravenous (i.v.) anesthetics, EC_{50} (effective concentration) has been defined as the blood concentration necessary to prevent movement in response to surgical stimulation in 50 % of subjects (Scheinin, 1999; Jones, 2000). Significant interindividual differences exist in drug distribution and entry into the effector site (Scheinin, 1999). This, in addition to the obvious difficulties in obtaining the concentration values in a clinical situation, makes even EC_{50}-values unsuitable for monitoring an individual patient.

2.5.2.2. Potent volatile anesthetic agents

MAC_{awake} values for desflurane, isoflurane, and sevoflurane are roughly 33-35 % of the MAC $_{skin\ incision}$ value of the anesthetic. MAC_{awake} values of halothane and N_2O are 52-58 % of their MAC $_{skin\ incision}$ values. Therefore, desflurane, isoflurane, and sevoflurane may be considered more potent amnestic anesthetics than halothane (Eger, 2001).

A MAC_{awake} of 2.6 % has been estimated for desflurane based on a volunteer study (Chortkoff *et al.*, 1995). Desflurane has been found to suppress both implicit and explicit memory formation at a concentration of 0.6 $MAC_{skin\ incision}$ (Gonsowski *et al.*, 1995).

Conscious memory was suppressed by administration of 0.45 $MAC_{skin\ incision}$ of isoflurane to a population of 17 volunteers. The EC_{50} for isoflurane for preventing conscious memories was 0.20 $MAC_{skin\ incision}$ in the study (Dwyer *et al.*, 1992). Isoflurane has also been reported to suppress both implicit and explicit memory formation at a concentration of 0.6 $MAC_{skin\ incision}$ (Gonsowski *et al.*, 1995).

A low concentration of sevoflurane (0.3 % and 0.6 %, end-tidal) produced a greater degree of amnesia, psychomotor impairment and drowsiness than 15 % and 30 % end-tidal N_2O, which was equipotent with the sevoflurane concentration in terms of MAC (Galinkin *et al.*, 1997). Based on mid-latency auditory evoked potential (MLAEP) studies, end-expiratory concentrations of sevoflurane greater than 1.5 % should suppress auditory perception, memory formation and implicit and explicit recall (Schwender *et al.*, 1996).

2.5.2.3. Intravenous anesthetics

$EC_{50awake}$ values for propofol (measured as blood concentration) follow the same pattern as for volatile anesthetics, $EC_{50awake}$ being 40 % of the $EC_{50skin\ incicision}$ of propofol (Jones, 2000). A case of awareness with recall has been reported, where propofol was used as a sole anesthetic in a microlaryngeal procedure. The induction dose of propofol was 2.1 mg/kg and the maintenance dose was 200 µg/kg/min (Kelly, and Roy, 1992).

Thiopental increases the latency and decreases the amplitude of the MLAEPs. The change is comparable to that seen with e.g. propofol and potent inhalational anesthetics (Schwender, Klasing *et al.*, 1994). Wilder-Smith *et al.* (1995) compared EEG arousal reactions during intubation in patients randomized to have anesthetic induction with either thiopental 6 mg/kg or propofol 3 mg/kg. The degree of cortical EEG depression was similar in both groups, but the degree of EEG arousal reactions was significantly lower in the propofol group.

In a study by Baraka *et al.* (1989), induction of anesthesia for an elective caesarean section with ketamine 1.5 mg/kg produced significantly lower incidence of reactions in the isolated forearm (70 % vs. 13 %, $p<0.05$) than thiopental 4 mg/kg. There was, however, no difference between the groups in recall of awareness in the postoperative interview.

Ketamine does not seem to produce changes in MLAEP amplitudes or latencies (Schwilden, 1994). This seems to imply that the primary processing of the auditory sensory information remains intact, but that there is disruption of sensory processing at a higher level reflected by EEG changes (Schwilden, 1994). Ketamine also has been shown to disrupt the memory retrieval process unlike many other drugs (Ghoneim, and Block, 1992).

2.5.2.4. Opioids

There are case reports of awareness during general anesthesia with very high doses of fentanyl (72-96 µg/kg) (Mummaneni *et al.*, 1980; Hilgenberg, 1981; Mark, and Greenberg, 1983), and it may therefore be regarded that opioids alone cannot guarantee surgical anesthesia (Wong, 1983).

2.5.2.5. Benzodiazepines

Benzodiazepines (diazepam, midazolam, and lorazepam) have been used for the maintenance of anesthesia in cardiac surgical patients. The dose of benzodiazepines, or opioids, did not differ between patients with and without awareness and recall (Phillips *et al.*, 1993).

In a study of the frequency of awareness with recall during arthroscopy, patients received either placebo or midazolam 15, 30, or 45 µg/kg i.v. in the operating room before the induction of anesthesia. Anesthesia was induced and maintained with propofol which was titrated to maintain heart rate and systolic blood pressure within ± 20 % of preoperative values. There were four patients with awareness (19.1 %) in the group of 21 patients receiving placebo), while the incidence of awareness was 2/69 (2.9 %) in the groups receiving midazolam ($p < 0.04$) (Miller *et al.*, 1996).

A group of cardiac surgical patients received flunitrazepam 0.01 mg/kg for the induction and 1.2 mg/h for maintenance of anesthesia. There was only a slight increase in the latency or decrease in amplitude of MLAEPs. These patients also reacted to loud sound (the sound of the sternotomy saw) with an increase in heart rate, arterial pressure, and pulmonary capillary wedge pressure. These changes where not noticed in two groups of patients whose anesthesia was induced with etomidate, and maintained with isoflurane, or propofol, respectively (Schwender, Haessler *et al.*, 1994).

2.5.2.6. Nitrous oxide

Conscious memories were not totally abolished by 0.6 MAC of N_2O in a population of 17 volunteers. The EC_{50} for N_2O in preventing conscious memories was estimated to be 0.50 $MAC_{\text{skin incision}}$ (Dwyer *et al.*, 1992). Similarly, it has been shown that cortical auditory evoked potentials (AEP) were suppressed significantly less by N_2O at 0.6 $MAC_{\text{skin incision}}$ than by isoflurane at 0.6 $MAC_{\text{skin incision}}$ (Newton *et al.*, 1989). There is evidence that N_2O may even antagonize the suppression of learning induced by isoflurane (Chortkoff *et al.*, 1993), as well as EEG depression caused by isoflurane (Yli-Hankala *et al.*, 1993).

In a study by Russell, the incidence of wakefulness as assessed by the isolated forearm method was 44 % in the group receiving 66 % N_2O in oxygen for the maintenance of anesthesia. The incidence of wakefulness was 7 % in the group receiving etomidate 10 µg/kg/min. The incidence of awareness with recall was 4 % in the group receiving N_2O for maintenance, and zero in the etomidate group (Russell, 1986). A conclusion was reached in a recent study that an anesthetic consisting of N_2O and bolus dosing of an opioid carries an unacceptably high risk of awareness and recall. The incidence of awareness with recall in the group of patients receiving 70 % N_2O supplemented with fentanyl boluses was six percent (Ghoneim *et al.*, 2000).

There is, however, a study of 138 patients none of whom reported awareness with recall after thiopental 7 mg/kg for induction followed by 66 % N_2O. The patients underwent various abdominal procedures with a mean duration of anesthesia of 80 minutes. Recall was tested with three consecutive structured interviews immediately after awakening and at 30-45 min and 3-4 h later(Agarwal, and Sikh, 1977).

The effect of N_2O, which is, at room temperature, a gas, is dependent on its partial pressure. Therefore, the effect of N_2O is reduced at high altitudes. Considering the earth's surface, a vast population lives, and is anaesthetized, at high altitudes (James, 1994).

2.5.2.7. Neuromuscular blocking agents

Most cases of awareness are recorded during so-called balanced anesthesia which includes the use of NMBs. Therefore, it is often recommended that NMBs be used as sparingly as possible (Mainzer, 1979; Ponte, 1995). There are, however, a small number of case reports of awareness in patients who received no NMBs at all (Saucier *et al.*, 1983; Osborne *et al.*, 1993; Cundy, 1995; Sandin *et al.*, 2000).

2.6. Prevention of awareness with recall

2.6.1. General recommendations

Several authors have expressed as a goal the prevention of awareness with recall during general anesthesia by all possible means

(Anonymous, 1976, 1980)

Several recommendations have been published on avoiding awareness with recall. These usually include avoiding or limiting muscle relaxant use (Hug, 1990; Lunn, and Rosen, 1990; Ghoneim, 2000), defining therapeutic windows for anesthetics, and also, defining factors modifying those windows (Hug, 1990).

There are recommendations not to rely solely on N_2O, but to supplement it with a volatile agent concentration of at least 0.6 % MAC $_{\text{skin incision}}$ (Lunn, and Rosen, 1990; Ghoneim, 2000), to administer at least 0.8-1 MAC $_{\text{skin incision}}$ when volatile anesthetics are used alone, and to use drugs that produce amnesia when only light anesthesia is tolerated (Ghoneim, 2000).

2.6.2. Methods of monitoring consciousness during general anesthesia

Many methods have been used to monitor the anesthetic state, especially to detect an insufficient depth of general anesthesia. These methods do not measure learning or possibility for later recall, but consciousness. There is a thorough review of the methodology by Heier and Steen (1996), and an update including the most recent methods by Drummond (2000).

2.6.2.1. Clinical signs

When anesthesia becomes too light, the patient may move or show signs of sympathetic activity. Movement is obviously not possible if large doses of NMBs have been used. Moreover, not all patients with intraoperative awareness move during the procedure (Saucier *et al.*, 1983; Cundy, 1995).

Signs of sympathetic activity: tachycardia, hypertension, sweating, pupillary dilatation, lacrimation and sweating are often used as clinical signs of an inadequate level of anesthesia. However, the signs of increased autonomic activity may be absent during treatment with many drugs: opioids, cholinergic and beta-adrenergic antagonists, vasodilators, and antihypertensive agents (Ghoneim, and Block, 1992). Epidural anesthesia may also obtund the sympathetic responses (Schwender, Faber-Zullig *et al.*, 1994). Furthermore, it seems that not all patients with intraoperative awareness, even with pain, show signs of increased sympathetic activity. In one study, propofol infusion was controlled to keep heart rate and systolic blood pressure within ± 20 % of the patient's preoperative values. However, a 19 % incidence of awareness and recall of was found in one of the study groups (Miller *et al.*, 1996).

Scoring methods have been developed for measuring the anesthetic state based on sympathetic activity (Evans, and Davies, 1984). However, the correlation of these scores with other measures of the anesthetic depth has been poor (Russell, 1993). Neither was a group of experienced anesthesiologists able to discriminate between patients with and without awareness in a study by Moerman and colleagues (Moerman *et al.*, 1993).

2.6.2.2. The isolated forearm technique

The technique of isolating one forearm from circulation before giving NMBs is described by Tunstall in 1977 (Tunstall, 1977). After induction of general anesthesia by anesthetic drugs but before giving NMBs, a blood pressure cuff is inflated on one arm to isolate that forearm from the circulation. The forearm remains isolated from the effects of NMBs once these drugs are administered, and therefore, the patient may use the isolated forearm e.g. for signaling. The method is limited by the ischemia produced by the inflated blood pressure cuff. However, the tourniquet may be pressurized several times consecutively if one assures that the concentration of NMBs is low at the time of deflation. The patient may respond by voluntary movement of the isolated forearm to questions posed by the investigator. Most of the patients responding by intraoperative forearm movement have no recall afterwards. IFT has been reported to be an unhelpful indicator of patients with awareness and postoperative recall (Bogod, 1990). Indeed, it has been shown that the responses of the isolated forearm, though representing complex responses to verbal commands, may not necessarily represent a conscious response (Thornton, and Jones, 1993). Some authors have found the method impossible to use because it interferes with the surgical activity (Breckenridge, and Aitkenhead, 1981).

2.6.2.3. Electroencephalography

The electroencephalogram (EEG) is the summary result of the activity of the cortical neurons (Bailey, and Jones, 1997). In general, there is a decrease of the fast activity and an increase in the high-amplitude, slow-frequency components in the EEG during anesthesia (Bailey, and Jones, 1997). However, the magnitude of change and exact patterns vary between anesthetic agents (Clark, and Rosner, 1973). Furthermore, there is considerable interference in the EEG recording caused by different electrical devices present in the operating room environment (Rampil, 1998). Therefore, raw EEG is not very suitable for assessing anesthetic state, at least in inexperienced hands.

Many forms of processed EEG signal have also been evaluated for the monitoring of depth of anesthesia. At least the following methods have been used: spectral array, period-amplitude analysis, spectral edge frequency, median frequency, and aperiodic analysis (Rampil, 1998). None of these methods have proven to be of practical value in monitoring the anesthetic state produced by anesthetic drug combinations (Ghoneim, and Block, 1992; Bailey, and Jones, 1997).

The bispectral index (BIS) is an empirically derived algorithm that reflects the state of the brain in relation to sedation (Sigl, and Chamoun, 1994; Rosow, and Manberg, 1998). It was developed by a statistical analysis of a large number of EEG samples on subjects whose level of sedation was known. BIS incorporates power spectral analysis of the EEG, components of the EEG that are due to phase relationships, and the degree of burst suppression (Rampil, 1998; Drummond, 2000; Kerssens, and Sebel, 2001).

The BIS seems to function well as a practical clinical on-line trend monitor of the level of sedation. The correlation of conscious responses and memory function at a population level is good, but there are considerable interindividual differences in these parameters, particularly at the lower end of the scale (Drummond, 2000; Kerssens, and Sebel, 2001).

The principle of auditory evoked responses (AER) is that the subject listens to 'click'-stimuli while his EEG is recorded, and an average response, the AER, is extracted from the background EEG that, in this context, is considered noise (Thornton, and Sharpe, 2001). The mid-latency auditory evoked potentials (MLAEP) are recorded 15-100 ms after the stimulus, and represent the primary non-cognitive cortical processing of auditory impulses (Heier, and Steen, 1996). All volatile anesthetics, propofol and thiopental reduce the amplitudes of MLAEPs and increase their latency in a dose-dependent fashion (Heier, and Steen, 1996; Yli-Hankala, 2000).

A correlation between short latencies of the auditory evoked signal and signaling of awareness by the isolated forearm method has been shown (Thornton *et al.*, 1989).

It has been shown that when the early cortical potentials of MLAEPs are preserved during general anesthesia, auditory information may be processed and remembered postoperatively (Schwender, Kaiser *et al.*, 1994). However, AER does not predict movement to noxious stimulation during 1 $MAC_{\text{skin incision}}$ concentration of isoflurane and N_2O (Kochs *et al.*, 1999). Thus, AER reflects the conscious state of the patient in relation to anesthesia and surgical stimulation and not solely in relation to anesthetic depth.

2.7. After-effects of awareness with recall during general anesthesia

2.7.1. Mental after-effects

The potential for mental consequences after neuromuscular paralysis was first described by Meyer and Blacher in 1961 in cardiac surgery patients (Meyer, and Blacher, 1961). The main features of the patients were anxiety, irritability, and repetitive nightmares. However, the patients did not have clear recollection of intra-operative awareness, and they were uncertain of the cause of their symptoms.

Mental after-effects are due to the very stressful experience of awareness during general anesthesia. It is, however, difficult for the patient to distinguish between periods immediately before and after anesthesia and the anesthesia itself. Patients have been described who claim to have been aware during anesthesia, even though only sedation or local anesthesia had been used. After-effects have been similar to those after awareness during intended general anesthesia (Moerman *et al.*, 1993; Cundy, 1995). This also applies to awareness and recall during waking up from an anesthesia: the time scale of the patient is distorted, and a patient may have serious psychiatric sequelae after recalling waking up intubated and during transport, even though he is no longer anesthetized from the standpoint of the anesthesiologist (Ho, 2001). It has also been claimed that awareness *per se* is not the important issue but rather, the sense of passively experiencing something over which one has no control, where the feeling is that things are not going as expected, and yet, they cannot be corrected by calling for help (Blacher, 1984). Muscle relaxation (Wang, 2000), pain and fear of dying (Cundy, and Dasey, 1996) have been cited as worst stressors causing the after-effects. Furthermore, it has been suggested that patients who have been forewarned of the possibility of being aware during surgery, and of the reasons for it, may not develop psychiatric after-effects (Holt, and Yate, 1993). In patient satisfaction studies, dissatisfaction scores are typically extremely high in cases of awareness with recall during general anesthesia (Myles *et al.*, 2000).

Typical symptoms after an experience of awareness during general anesthesia are irritability, insomnia, repetitive nightmares, anxiety, depression, and preoccupation with death. There may also be morbid fear of hospitals or doctors, and of the need for future surgery (Blacher, 1975, 1984; Payne, 1994). The patients also typically find it difficult to discuss their experience of awareness (Blacher, 1975). This may be made worse by the medical and nursing staff if it is suggested that the experience had been imagined, or, even worse, the patient is blamed for it because of e.g. overweight (Payne, 1994). When a patient reported an experience of awareness during anesthesia to the hospital staff 37 % of the personnel responded with disbelief, ignorance, or anger. An additional 14 % of patients were told that their experience was “just a bad dream”, “all in your imagination”, or that they “were mad or hallucinating”, or “had a seventh sense” (Cobcroft, and Forsdick, 1993).

In the study of Moerman *et al.* (1993), 70 % of patients who had experienced awareness during general anesthesia had unpleasant after-effects; 6 % of patients had needed psychotherapeutic help. In the study by Shwender and co-workers 48.9 % of the patients had after-effects, anxiety (55.0 %) and nightmares (52.4 %) being the most common ones. Post-traumatic stress disorder (PTSD) was found in 14.3 % (Schwender *et al.*, 1998). Both studies recruited patients by advertising or via referral from colleagues.

Of the long term after-effects, the most important is PTSD. PTSD is characterized by three symptom clusters: 1) re-experiencing, 2) avoidance and numbing, and 3) increased arousal which follows a traumatic event (Osterman, and Van Der Kolk, 1998). PTSD is chronic or recurring in a high proportion of those in whom it develops (Osterman, and Van Der Kolk, 1998). In a prospective study, four out of six patients had mental reactions after a year of the precipitating anesthesia (Bergström, and Bernstein, 1968), and in another study 56.3 % of the subjects with intraoperative awareness had PTSD after a mean of 17.9 postoperative years (Osterman *et al.*, 2001). In a prospective follow-up study, all eight patients with intraoperative awareness experienced fear when falling asleep from time to time. All had anxiety concerning future anesthetics (Jordening, and Pedersen, 1991). A recent study (Lennmarken *et al.*, 2002) tried to evaluate all patients with previously experienced awareness and recall found in another large study (Sandin *et al.*, 2000). The investigators were able to interview nine of the 18 original patients. Four of the nine interviewed patients fulfilled all DSM-IV criteria for PTSD median of 27 months after the unsuccessful anesthesia. Three other patients had some PTSD symptoms, but did not fulfill the diagnostic criteria. Six of the original 18 patients refused the interview, which the authors partly interpret as avoidance behavior typical of PTSD (Lennmarken *et al.*, 2002).

Recommendations for treating a patient who has just experienced awareness with recall have been published. The anesthesiologist should always visit the patient complaining awareness with recall and acknowledge patient's account of events as real. The anesthesiologist should apologize to the patient and assure that the event will be recorded in the hospital notes. A possible error that has lead to the event of awareness with recall should be admitted (Aitkenhead, 1990; Ghoneim, 2000). It is also suggested that a patient with intraoperative awareness needs to feel a sense of safety and connection to the surgical and anesthesia teams (Osterman, and Van Der Kolk, 1998). Care should be taken not to ascribe blame on the patient. However, it is the opinion of some authors that explanation and simple reassurance are not adequate measures for preventing serious psychiatric complications of awareness with recall (Macleod, and Maycock, 1992). Indeed, based on the possibly large incidence of PTSD after, at least, painful awareness (Osterman *et al.*, 2001), and the chronic nature of PTSD, a psychiatric consultation is usually warranted in these cases (Osterman, and Van Der Kolk, 1998; Lennmarken *et al.*, 2002).

2.7.2. Medico-legal after-effects

Very large compensations, GBP 20,000 to 100,000, have been awarded for awareness during general anesthesia in Great Britain (Payne, 1994). In one of the cases, the compensation was particularly large, in part, because the anesthesiologists refused to see the patient after surgery even though she complained about her awareness (Payne, 1994). In the malpractice claims involving awareness during general anesthesia in the United States, the cost of settlement or jury awards have ranged from USD 1,000 to 600,000 (Domino *et al.*, 1999). In this analysis, factors associated with claims for recall during general anesthesia compared to other general anesthesia claims were: no volatile anesthetic agent used, female gender, obstetric or gynecologic procedure, intraoperative opioid, and intraoperative muscle relaxant (Domino *et al.*, 1999).

No precedent based on a case of intraoperative awareness and recall has been issued by the Finnish Supreme Court according to the Finlex database kept by the Ministry of Justice of Finland (Anonymous, 2002).

3. Aims of the study

1. To study the incidence of awareness with recall during anesthesia for general surgery. (Study1)

2. To study the incidence of awareness with recall during anesthesia for cardiac surgery. (Studies 1 and 2)

3. To find out possible differences in anesthetic drug dosing between patients with and without awareness and recall (Studies 1 and 3)

4. To study whether or not it is possible to detect awareness with recall by analyzing changes in variables commonly monitored during general anesthesia with conventional statistical methods or artificial intelligence neural networks. (Study 4)

5. To evaluate the utility of giving feedback information to the anesthesiologists in lowering the incidence of awareness. (Study 2)

6. To study the psychiatric consequences of awareness with recall. (Studies 1,2,3 and 5)

7. To study the medico-legal consequences of awareness with recall in Finland in the form of patient insurance claims. (Study 5)

4. Patients and methods

4.1. Patients

These studies were carried out at the Päijät-Häme Central Hospital, Lahti, Finland (Study 1), and the Meilahti Hospital Department of Surgery, Helsinki University Central Hospital, Helsinki, Finland (Studies 2 and 3). In addition, patient records were obtained through the Patient Insurance Association (PIA) of Finland and through advertisements in the Journal of the Finnish Society of Anaesthesiologists (Finnanest 1997: 30: 38). The total number of enrolled patient cases was 3,868 (1,485 male and 2,383 female). Taking into account the fact that some patients had been operated more than once, the total number of individuals included in these studies is 3,739 (1,463 male, 2,276 female). Permissions of local ethical committees were obtained for the studies. The number of cases in the individual Studies is shown in Figure 1.

In Study 1 all elective general surgery patients over 12 years of age operated between August 1994 and August 1995 in the Päijät-Häme Central Hospital, Lahti, Finland were included in the study. A total of 4,818 (1,215 male, 3,603 female) such patients were operated on during the study period, and 2612 (54.2 %, 608 male, 2,004 female) of them were interviewed. 121 of the included patients were operated more than once, and hence, interviewed more than once. Therefore, the total number of different patients included is 2,484 (586 male and 1,898 female). Failure to enter all elective patients into the study resulted from time constraints imposed by other duties on the anesthesia nurses who did the screening interviews.

In Study 2, a random sample of 99 (74 male, 25 female) patients who underwent open heart surgery between June, 1992 and September, 1992 was selected first. The second part of study included all open heart surgery patients operated on between September, 22 and November, 23, 1993, altogether 236 patients. Thirty two patients were excluded, leaving 204 (86%; 147 male, 57 female) for the analysis. Excluded were those transferred to other hospitals before the screening interviews, patients with Intensive care unit (ICU) stays over ten days, patients with neurological complications making the screening interview impossible, and patients who did not survive until the interview. The total number of patients in Study 2 was 303 (221 male, 82 female).

In Study 3, all open heart surgery patients operated on between January 13, 1995 and January 13, 1996 were evaluated for enrollment. There were 1,218 (870 male, 348 female) such patients, and 929 (76%; 653 male, 276 female) of those were included in the study. The reasons for exclusion were: 148 patients could not be reached before they left the ward after the operation, 62 stayed in the

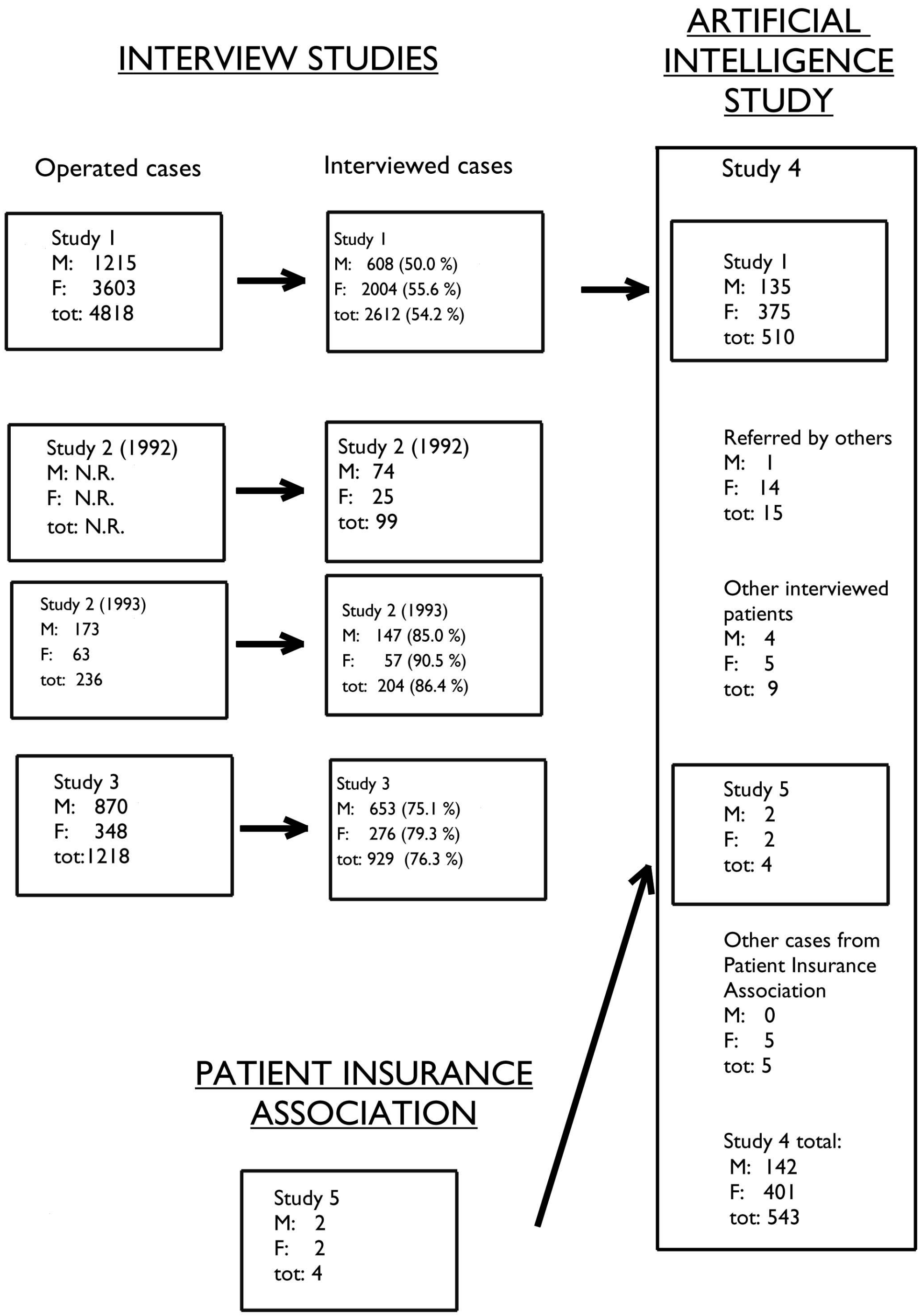

Figure 1. Number and flow of patients in the studies. Operated and actually interviewed cases (interview percentage) are shown for the interview studies 1, 2, and 3. Use of patient cases from these and other sources for the artificial intelligence study (4) are shown by arrows.

ICU for more than 5 days, 38 died before the interview, 25 developed neurological symptoms preventing the screening interview, 6 did not speak Finnish, 2 had psychiatric syndromes preventing interview, and 7 had various other reasons preventing interview.

In Study 4, patients with awareness and recall were recruited from Study 1 (n = 9, 2 male, 7 female), Study 5 (n = 4, 2 male, 2 female), from claims filed in the PIA (n = 5, all female), and from information received from colleague anesthesiologists (n = 15, 1 male, 13 female, one of whom had experienced awareness twice). The total number of patients with awareness and recall was, therefore, 33 (5 male, 28 female). The control patients (n = 510, 137 male, 373 female) were randomly gathered from the patients without conscious awareness and recall in Study 1 (n = 501, 133 male, 368 female) and from patients interviewed after general surgery in Meilahti Hospital (n = 9, 4 male, 5 female). Altogether, in Study 4, there were 543 (142 male, 401 female) patient cases, and 542 individuals (142 males, 400 females).

In Study 5, there were 4 patient records collected from the claims of compensation filed in the PIA between May 1, 1987 and December 31, 1993. Two of these patients were male and two female.

4.2. Interviews and classification

The screening interviews used questions described earlier (Brice *et al.*, 1970, Table 1) and the patients were interviewed only once. In Study 1, the interviews were conducted by recovery room nurses before the patient left the recovery room. The nurses notified the investigators immediately of clear cases of intraoperative awareness. After the completion of the studies, the interview forms completed by the nurses were analyzed by the investigators. The cardiac surgery patients in studies 2 and 3 were interviewed in the postoperative wards by the investigators.

When interpreting the answers to the structured interview questions, importance was placed on the subjective feeling of the patient regarding awareness during anesthesia. The answers were also graded to three groups according to objective memories that could be traced back to the time of anesthesia, and the duration of awareness (Table 6).

Table 6. Grouping of structured interview answers.

Group	*Definition*
Group 1	Patients with unclear memories or dreams, which could be of intra-operative origin.
Group 2	Patients with short periods of awareness occurring either intraoperatively or during the period of awakening from anesthesia.
Group 3	Patients with long-lasting, clear, and undisputed recall of the intraoperative period.

4.3. Medications

Anesthesia records were used as a source of information regarding the anesthetic medications used during the studies. In Studies 1, 2, and 3 the total dose of medications given i.v. was recorded. The dose of the inhaled anesthetics was calculated from the anesthetic records as follows: The inspired concentration of the anesthetic was multiplied by the time (in minutes) that this concentration was used; the concentration-time products were then added to a grand total. The anesthetic time was recorded, and a mean dose of both i.v. and inhaled anesthetic agents was calculated. Furthermore, continuous or intermittent anesthetic delivery was also noted. Continuous administration of an anesthetic was defined as an inhaled or i.v. anesthetic started within 15 minutes after induction and continued until the end of surgery without interruptions lasting longer than 15 min.

In Study 1, the doses of anesthetics used for general anesthesia were estimated from random samples collected as follows: First, a sample of 103 anesthetic records was collected from the three-month period immediately preceding the interview period. We assume that this period represents the standard practice of the anesthesiologists in the hospital. During each four three-month interview periods, a sample of 108 anesthetic records was collected. Thus, we had a database of 535 random anesthetic records, which allowed detection of possible change in the doses of anesthetics over time, and comparison between doses received by patients with or without awareness. This database was also used for Poisson regression analysis. When comparing the doses of anesthetics received by the patients with or without awareness, the records of patients not interviewed for some reason were excluded. After this exclusion, 247 records were left for analysis.

In Study 2, the anesthetic records of all interviewed patients were included in the analysis.

In Study 3, a random sample of 308 anesthetic records was selected from the group of interviewed patients. Later, the anesthetic records of 16 patients with awareness and five patients with unpleasant dreams were included. Thus the total number of anesthetic records used for the analysis of medications was 329.

In Study 5, the anesthetic records of all four patients were analyzed.

4.4. Artificial neural networks

Artificial neural networks are a form of artificial intelligence with the ability to discover non-linear dependencies between input and output patterns even when they are difficult or impossible to detect with conventional statistical methods. In practice, an artificial neural network is simulated in a computer program and is configured and trained to perform a specific task. A network is trained by presenting examples of input records with correct output from a training data set. The network 'learns' to associate a given input with correct output by altering its internal weights. A successfully trained network can correctly classify input patterns that are similar, but not necessarily identical to the training patterns

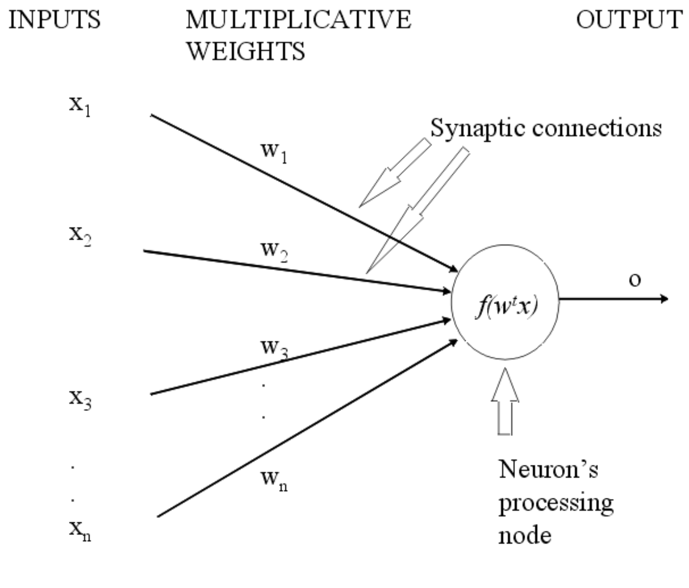

Figure 2. General representation of an artificial neural network neuron consisting of a processing node and synaptic input and output connections.

(Veselis *et al.*, 1991; Zurada, 1992; Cross *et al.*, 1995).

There are many different types of artificial neural models that use different configurations and learning rules (Zurada, 1992). A schematic representation of an artificial neuron is shown in Figure 2.

The neuron output signal is given by the following general rule:

$$o = f(w^t x) \qquad (1)$$

or

$$o = f\left(\sum_{i=1}^{n} w_i x_i\right) \qquad (2)$$

where w is the weight vector and x is the input vector. All vectors defined here are column vectors, and superscript t denotes a transposition. The function $f(w^t x)$ is called the activation function (Zurada, 1992).

In this thesis, the hidden and output neurons of the neural models follow continuous nonlinear activation functions of the type:

$$o_j = \frac{1}{1 + e^{-\sum_i w_{ji} o_i + w_j \theta}} \qquad (3)$$

where o denotes output of a neuron, w_{ji} denote connection weights, o_i denotes the output of a neuron in the previous layer, $w_j \theta$ denotes the adjustable threshold for the neuron, i denotes the number of inputs to the neuron from the previous layer and j denotes the current neuron (Anonymous, 1998).

Training of the network in this study followed the delta learning rule, and first involved initializing the connection weights to small random numbers. The network then calculated its own output value from the first input record and compared this to the target value presented to the output neuron. The difference was the error signal. If there was no error then no learning took place. Otherwise, the interconnecting weights were changed to reduce the error by an amount proportional to the product of the error signal and the first derivative of the nonlinear activation function (the delta learning rule; Zurada, 1992; Anonymous, 1998):

$$r = [d_i - f(w_i^t x)]\, f'(w_i^t x) \qquad (4)$$

Neural networks have been used in various applications in clinical medicine. Examples are diagnostic problems (appendicitis, myocardial infarction, pulmonary embolism), image analysis, waveform analysis (ECG, EEG), and outcome prediction. Best artificial neural models have performed as well, or better, than experienced clinicians (Baxt, 1995).

In Study 4, artificial neural models were used for analyzing the physiologic data in the following fashion: All individual data points for heart rate, systolic and diastolic blood pressure, end-tidal carbon dioxide ($PetCO_2$) concentration, and arterial blood oxygen saturation (SpO_2) throughout the duration of each anesthetic were entered manually from the anesthesia records into a database, along with age, gender, weight and height. Maximum, minimum and mean values of these variables were calculated for each patient. The use of anticholinergic or sympathetic agonist medication may influence the measured physiologic parameters. Therefore, the dose (mg/kg) of atropine, ethilephrine, or ephedrine given to patients with or without awareness was analyzed and compared with Mann-Whitney test.

The artificial neural networks were configured using commercially available neural network software (NNModel32®, Neural Fusion, New York, NY) running on a desktop computer. The variables used in the analysis, were first normalized using the NORMDIST function in Microsoft Excel 5.0 spreadsheet (Microsoft Corporation, Redmond, WA) and subsequently divided to training and testing data sets in a random fashion. The training data set consisted of 412 patients without awareness and 20 patients with awareness. The complete data of the 20 patients with awareness were multiplied fivefold resulting in a training database of 100 records with awareness, and 412 without awareness. These records were presented to the neural network program in a random order. The remaining data of 13 patients with awareness and 98 patients without awareness were reserved for the testing of the trained network.

We used a three-level back-error propagation neural network model, fully interconnected between layers (Zurada, 1992; Cross *et al.*, 1995). The summary functions of the physiologic and demographic parameters in different combinations formed the input values to the network, and the outcome was reported by a single continuous-function output neuron designating target 1 = awareness and 0 = no awareness. The number of neurons in the intermediate (hidden) layer of the network was changed between three and ten. A learning rate of 0.75 and a momentum constant $\alpha = 0.8$ were used for all neural models (Haykin, 1999). The training data matrix was presented to the network 1,000 times or until error tolerance of ±5 % of the total error was reached, whichever came first. The resulting models were analyzed by feeding the test data matrix values into the network.

The success of randomization of patients into training and testing groups was evaluated by comparing these groups with chi-squared and Student's t-tests. The goodness of the neural models in indicating awareness with recall in the testing data set were estimated by calculating the sensitivity and specificity of any given model. Subsequently, the likelihood ratio was calculated as

$$LR = \frac{sensitivity}{1 - specificity} \qquad (5)$$

The best neural models were chosen using the likelihood ratio as the criterion. The models generated by the study were compared with the Mann-Whitney test.

The positive and negative predictive values of the test were calculated using the Bayes' theorem (Altman, 1991). The prevalence of the condition of interest necessary for this calculation was assumed to be 0.5%. Also, prediction probability (P_k) as suggested by Smith *et al.* (1996) was calculated for the neural models.

The training of the neural models includes reduction of error. The success of this process may be estimated by calculating the root-mean square normalized error:

$$E_{rms} = \frac{1}{PK}\sqrt{\sum_{p=1}^{P}\sum_{k=1}^{K}(d_{pk} - o_{pk})^2} \qquad (6)$$

where P is the number of training patterns, K is the number of outputs, d is the desired (target) output, and o is the observed output (Zurada, 1992).

Classifying networks, like those in the present study, may further be evaluated in the classifying task by calculating the decision error of the network:

$$E_d = \frac{N_{err}}{PK} \qquad (7)$$

where N_{err} is the total number of bit errors resulting at K thresholded outputs over the complete training cycle (Zurada, 1992).

4.5. Feedback information

In Study 2, feedback information for the cardiac anesthesiologists was used to examine the effect of that information as a possible way of reducing the incidence of awareness with recall. The feedback consisted of general information of possibilities to reduce conscious awareness during general anesthesia. Written information of the same matter was also included in the education files of the clinic where the study was performed. This information recommends continuous use of either inhalation or i.v. anesthetic agents, monitoring of end-tidal concentrations of inhalation anesthetic agents, minimizing neuromuscular blockade, and encourages noticing clinical signs of light anesthesia. Also specific suggestions of dosages for some anesthetic agents commonly used in cardiac anesthesia were given.

4.6. Psychiatric interview and testing

In Study 1, the patients with awareness were recruited to a psychiatric interview, testing, and follow-up. Simultaneously matched control patients were included in similar psychiatric scrutiny. The matching was made for the following factors: age ± 5 years, sex, weight ± 5 kg, body mass index ± 3 %, type of surgery, date of surgery ± 3 weeks, and ASA physical status.

If the patients with the experience of awareness and the matched control patients were able and willing to give informed consent, they were interviewed by a psychiatrist immediately after the operation. If the patient had already left the hospital, the first interview was done over the telephone and the first face-to-face interview within two weeks after the operation. The patients were re-interviewed 2 and 6 months after the operation.

The interviewer was blinded to the presence of absence of awareness during the operation. All diagnoses were made according to strict DSM-III-criteria by using the Structured Clinical Interview for DSM-III-R Non Patient edition (SCID-NP) (Spitzer *et al.*, 1990a) and Structured Clinical Interview for DSM-III-R-Personality Disorders (SCID-II) (Spitzer *et al.*, 1990b).

Patients completed the Symptom-Checklist-90-Revised (SCL-90-R), a measure of psychological distress (Degoratis *et al.*, 1973). SCL-90-R was used to make the diagnostic structured interview complete. Patients were also asked to fill out the Impact of Event Scale (IES), a measure which indexes symptoms that characterize PTSD (Horowitz *et al.*, 1979).

4.7. Statistical methods

Differences in frequencies were compared with the chi-squared test (with Yate's continuity correction, as appropriate), except in Study 2 where Fisher's exact test also was used. For other paired comparisons, Student's t-test or the Mann-Whitney U-test was used, according to the distribution of the data. Analysis of variance (ANOVA) was used to detect statistical significance of changes in the use of medications over time (Study 1). *Post-hoc* comparisons were performed with Tukey's honestly significant test.

The Poisson regression model, a conventional statistical technique which allows an adjustment for a rare event such as awareness with recall, was used in Studies 1, 3 and 4. In the Poisson regression, the relationship between an observed count and a set of explanatory variables is analyzed with a Poisson distribution. For large n and small p, e.g., awareness with recall during general anesthesia, binomial probabilities are approximated by the Poisson distribution. The outcome (awareness or no awareness) formed the dependent factor in these regression models. Possible factors explaining intraoperative awareness were entered in the regression as independent factors. For significant explanatory factors, relative risk for one unit change of the explaining factor was calculated.

For some categorical comparisons of two groups with respect to the risk of awareness and recall, relative risk estimation was also used (Altman, 1991). 95 % CI based on the Normal distribution or the Poisson distribution, according to the distribution of the data, were also calculated.

For all statistical tests, a p-value less than 0.05 was considered statistically significant.

5. Results

5.1. The nature of the experience of awareness during general anesthesia

The patients with awareness and recall from all the Studies 1-5 are summarized in the Appendix. There were seventy patients who suffered from awareness and recall during general anesthesia. The anesthetics for these patients were administered between 1976 and 1998 with a median of 1994. Forty (57 %) of the patients were female, and thirty (43 %) male. The experience of these patients during the episode of awareness is summarized in Table 7.

5.2. Incidence of awareness with recall during general surgery

The incidence of awareness with recall during non-cardiac surgery procedures requiring general anesthesia is shown in Table 8

5.3. Incidence of awareness with recall during open heart surgery

The incidence of awareness with recall during

Table 7. Experiences during episode of awareness. Numbers of patients and percentages of those who responded to the question are shown.

	Recollection								
	Auditory	*Visual*	*Tactile*	*Pain*	*Tried to move*	*Able to move*	*Immediate understanding*	*Immediate anxiety*	*Awareness as the most unpleasant experience during operation*
Yes	42 (62.7)	12 (17.9)	43 (64.2)	22 (31.9)	28 (82.4)	6 (20.0)	53 (82.8)	29 (61.7)	7 (16.7)
No	25 (37.3)	55 (82.1)	24 (35.8)	47 (68.1)	6 (17.6)	24 (80.0)	11 (17.2)	18 (38.3)	35 (83.3)
Number responded	67	67	67	69	34	30	64	47	42
No response	3	3	3	1	36	40	6	23	28
Total	70	70	70	70	70	70	70	70	70

Table 8. Incidence of awareness during non-cardiac procedures requiring general anesthesia (Study 1).

Awareness Group	*Awareness / Number of interviews*	*Percentage (95 % CI)*
Group 1	9 / 2,612	0.34 (0.16-0.65)
Group 2	6 / 2,612	0.23 (0.08-0.50)
Group 3	4 / 2,612	0.15 (0.04-0.39)
Groups 2-3	10 / 2,612	0.38 (0.18-0.70)
Total	19 / 2,612	0.73 (0.44-1.14)

open heart surgery is shown in Table 9.

5.4. Differences in anesthetic drug dosing between patients with and without awareness

Possible differences in anesthetic agent dosing were studied using Poisson regression models. There were differences in the dosing of isoflurane and propofol during anesthesia for general surgery (Study 1), and midazolam during cardiac surgery (Study 3) as summarized in Tables 10 and 11, respectively.

5.5. Conventional statistical methods and artificial neural networks in detecting awareness from monitored physiologic variables

Artificial neural models and conventional statistical methods (Poisson regression) were compared in Study 4 in relation to their ability to discriminate between patients with and without intraoperative awareness. A total of 52 different neural models were tested. The two best neural models by their ability to identify patients with awareness in the test data set both had a likelihood ratio of 11.3. Their sensitivity and specificity in the discriminating task were 23 % and 98 %, respectively (Figure 3).

Both models had 20 input values: mean, minimum, maximum and number of recorded measurements for end-tidal carbon dioxide concentration, arterial blood oxygen saturation, systolic and diastolic blood pressure, and heart rate. The models had 7 and 8 intermediate layer neurons, and output ranges from -0.299 to 1.176 and from -0.331 to 1.090 in

Table 9. The incidence of awareness during open heat surgery.

Study	*Awareness Group*	*Awareness / Number of interviews*	*Percentage (95 % CI)*
Study 2, year 1992	Group 3	4 / 99	4.0 (1.1-10.3)
Study 2. year 1993	Group 2	1 / 204	0.49 (0.01-2.73)
	Group 3	2 / 204	0.98 (0.12-3.54)
	Total	3 / 204	1.5 (0.3-4.3)
Study 3, Year 1995	Group 1	16 / 929	1.72 (0.98-2.80)
	Group 2	4 / 929	0.43 (0.12-1.10)
	Group 3	1 / 929	0.11 (0.003-0.60)
	Groups 2-3	5 / 929	0.54 (0.17-1.26)
	Total	21 / 929	2.26 (1.40-3.46)

Table 10. Dose of anesthetic agents given to patients with awareness and recall (groups 1-3) and control patients during general surgery. The probability of the Poisson regression model as well as the relative risk derived from the model is also given.

	Patients with awareness			*Patients without awareness*				
		Dose			*Dose*			
Anesthetic	*n*	*Median*	*Range*	*n*	*Median*	*Range*	*p (Poisson regression model)*	*Relative risk for one unit change in dose*
Thiopental (mg/kg)	8	6.0	4.2-8.3	130	5.6	2.2-8.9	0.59	N.A.
Propofol (µg/kg/min)	10	73	23-357	90	228.2	22-760	0.03	0.99
Isoflurane (FiAA%/min[1)])	12	0.42	0.12-0.75	118	0.65	0.05-1.71	0.003	0.70
Enflurane (FiAA%/min[1)])	2	0.69	0.26-1.11	32	0.58	0.28-1.10	N.A.	N.A.
Fentanyl (ng/kg/min)	16	41	23-99	163	42.6	18-230	0.82	N.A.
Alfentanil (µg/kg/min)	3	1.2	0.6-1.8	57	1.54	0.2-4.0	N.A	N.A.
Atracurium (µg/kg/min)	13	9.3	4.4-12.4	149	8.1	2.4-67.3	0.72	N.A.
Diazepam as premedication (mg/kg)	6	0.14	0.07-0.19	131	0.15	0.07-029	N.A	N.A.

[1)] The inspiratory concentration that would have been delivered had the total dose of the volatile anesthetic agent been divided equally to the whole duration of anesthesia.

the test data set, respectively. The root-mean-square normalized errors for these models were 0.967 and 0.922, respectively. Decision errors in the training data set were 0 and 0.0098, respectively. In the test data set, the values indicated by the neural models were not different between groups of patients with and without awareness by Mann-Whitney test. The prediction probabilities P_k (SE) for the best neural models were 0.66 (0.08) and 0.60 (0.10), respectively. If we assume that the incidence of awareness with recall is 0.5 %, we can calculate a negative predictive value of 99.6 % for the artificial neural models.

The prognostic significance of the measured variables as analyzed with the Poisson regression are given in Table 12. In this analysis, high systolic blood pressure, high minimum diastolic blood pressure, and high mean and maximum heart rate were significant predictors of intraoperative awareness with recall.

5.6. The possibility of reducing the incidence of awareness by giving feedback information to the anesthesiologists

In study 2, the incidence of awareness fell (from 4 % to 1.5 %, ns.) after the cardiac anesthesiologists received general and feedback information about awareness during anesthesia. The relative risk of awareness and recall (95 % CI) in 1992 was 275 % (range 63 -

Table 11. Dose of anesthetic drugs during cardiac surgery given to patients with and without awareness and recall.

Anesthetic	*Patients with awareness*			*Patients without awareness*			*P (Poisson regression model)*	*Relative risk for one unit change in dose*
		Dose			*Dose*			
	n	*Median*	*Range*	*n*	*Median*	*Range*		
Diazepam (µg/kg/min)	11	0.47	0.24-0.96	113	0.60	0.11-2.01	0.149	N.A.
Lorazepam (µg/kg/min)	2	0.14	0.10-0.18	33	0.17	0.08-0.53	0.491	N.A.
Midazolam (µg/kg/min)	10	0.88	0.46-1.94	157	1.14	0.29-3.18	0.047	0.13
Propofol (µg/kg/min)	2	26.5	4.5-48.6	24	4.4	0.4-88.2	0.653	N.A.
Thiopental (µg/kg/min)	2	11.4	4.8-18.0	65	9.7	2.4-49.7	0.713	N.A.
Alfentanil (µg/kg/min)	1		1.01	35	1.45	0.29-3.99	0.319	N.A.
Fentanyl (µg/kg/min)	13	0.22	0.11-0.32	189	0.22	0.02-6.45	0.841	N.A.
Sufentanil (µg/kg/min)	7	0.04	0.02-0.05	79	0.04	0.01-0.18	0.711	N.A.
Pancuronium (µg/kg/min)	20	0.52	0.35-0.82	297	0.56	0.06-1.00	0.277	N.A.
Enflurane (FiAA%/min[1)])	7	0.12	0.09-0.63	91	0.37	0.04-0.87	0.106	N.A.
Isoflurane (FiAA%/min[1)])	13	0.34	0.14-0.60	205	0.33	0.02-0.95	0.789	N.A.

[1)] The inspiratory concentration that would have been delivered had the total dose of the volatile anesthetic been divided equally to the whole duration of anesthesia.

1204 %) of the risk in 1993. Simultaneously, the use of continuous infusions, or the use of a combination of an anesthetic infusion and inhalation, increased significantly, from 14 % of the anesthetics to 36 % (p<0.001) and 19 % to 56 % (p<0.001), respectively. Also, the doses of diazepam, fentanyl, and enflurane increased while doses of pancuronium decreased (Table 13).

In Study 1, there was an increase in the dosing of isoflurane over time during the course of the study. Simultaneously, a decreasing trend in awareness was noted. There were, however, no significant changes in the incidence of awareness over time during the study (Table 14).

5.7. Psychiatric consequences of awareness during anesthesia

In Study 1, seven patients with awareness and recall were evaluated for psychiatric interview and follow-up. Two patients had to be ex-

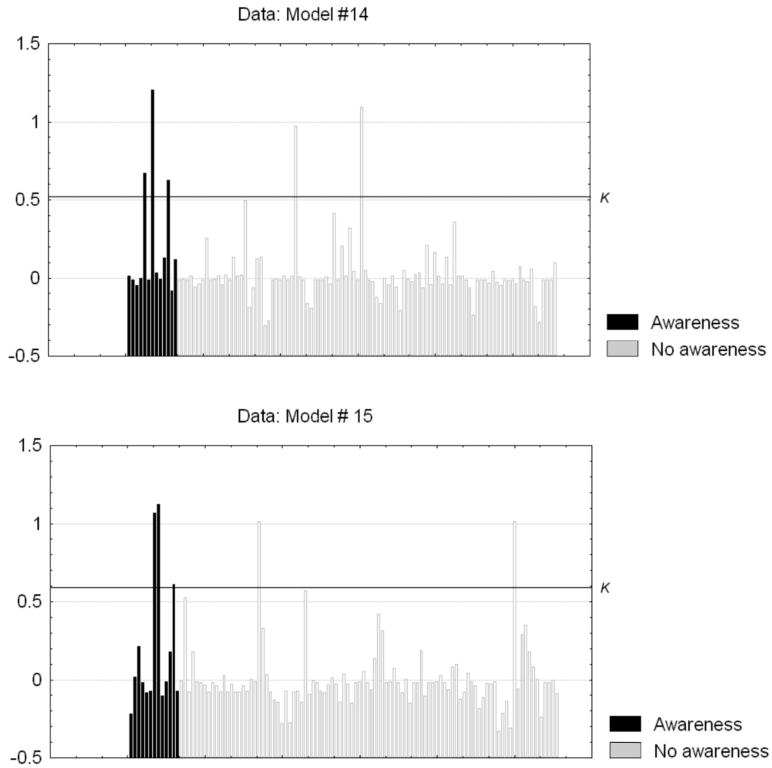

Figure 3. The values indicated by the two best neural model for each case of the test data set. Each individual bar in the graphs represents the value given by the neural model to each patient in the test data set. Patients with awareness are shown by black bars and patients without awareness are shown in gray. Value close to 1 indicates awareness with recall while value close to 0 indicates no awareness. The decision threshold (K) between awareness and no awareness is shown as a straight line.

cluded from the interview, one because he was in very poor physical condition and did not remember the experience of awareness, and the other because she was too incoherent to follow the structured psychiatric interview. One of the five remaining patients felt intense fear during the experience of awareness and had some sleep disturbances afterwards. However, she did not meet the criteria of PTSD. None of the other patients followed-up experienced any after-effects. Three of five patients with awareness had a history of major depression, and preoperative symptoms of depression and anxiety. None of the control group patients had any preoperative psychiatric disorders. The mental state of the two depressive patients did not significantly change after the operation, but one patient was treated with antidepressant medication and recovered.

5.8. Medico-legal consequences of awareness with recall in Finland

Four insurance claims concerning awareness during anesthesia were filed in the PIA between May 1, 1987 and December 31, 1993 (Study 5). This represents 0.02 % of all Patient Insurance claims (n = 23,363) filed during that period. Further cases were collected for Study 4: between Jan 1, 1994 and June 15, 1997 another seven claims, concerning awareness at least as a part of the complaint, were filed. The details of all these 11 cases with

Table 12. Demographic and monitored parameters for patients with awareness and recall and those without. Number of patients analyzed, median (ranges), and results of the Poisson regression model are given.

	Patients with awareness		*Patients without awareness*		*Poisson regression*	
	n	*median (range)*	*n*	*median (range)*	*p*	*Relative risk for one unit increase in the value of the variable*
Age (years)	33	37 (23-82)	510	43 (12-90)	0.20	
Sex (f/m)	28/5		373/137		0.16	
Height (cm)	31	168 (150-180)	507	167 (145-194)	0.73	
Weight (kg)	32	70 (28.5-112)	509	68 (40-142)	0.94	
Body Mass Index	31	24.5 (16.4-37.9)	507	24.4 (15.4-42.9)	0.74	
ET CO2 mean (%)	28	4.7 (3.7-6.0)	418	4.7 (3.6-6.2)	0.55	
ET CO2 minimum (%)	28	4.5 (3.4-6.0)	418	4.4 (3.2-6.2)	0.60	
ET CO2 maximum (%)	28	4.9 (3.7-7.8)	418	5.0 (3.7-6.8)	0.42	
SaO2 mean (%)	26	98 (92-100)	497	98 (82-100)	0.33	
SaO2 minimum (%)	25	97 (90-100)	496	97 (60-100)	0.90	
SaO2 maximum (%)	26	99 (96-100)	497	99 (94-100)	0.75	
Systolic BP mean (mmHg)	33	129 (75-201)	508	118 (80-206)	0.0005	1.03
Systolic BP minimum (mmHg)	33	108(55-180)	506	100 (55-175)	0.0022	1.03
Systolic BP maximum (mmHg)	33	150 (100-233)	508	145 (85-258)	0.0083	1.02
Diastolic BP mean (mmHg)	29	77 (42-123)	410	75 (48-140)	0.11	
Diastolic BP minimum (mmHg)	29	60 (34-112)	410	60 (35-105)	0.0395	1.03
Diastolic BP maximum (mmHg)	29	92 (56-152)	410	95 (55-145)	0.8563	
Heart rate mean (/min)	33	77 (58-117)	508	74 (50-120)	0.0288	1.03
Heart rate minimum (/min)	33	66 (43-105)	507	65 (40-105)	0.2521	
Heart rate maximum (/min)	33	95 (70-150)	508	90 (55-160)	0.0002	1.03

Table 13. Intravenous anesthetic agents used during the two years of Study 2; number of patients and dose (median and 90% (central range).

	1992	*1993*
Diazepam (μg/kg/min)	66 0.67 (0.21-1.16)	168 0.78 (0.24-1.57) ***
Lorazepam (μg/kg/min)	6 0.16 (0.12-0.19)	11 0.17 (0.12-0.30)
Midazolam (μg/kg/min)	12 1.2 (0.4-2.2)	41 0.8 (0.5-1.4) **
Thiopental (mg/kg/min)	44 0.010 (0.003-0.037)	75 0.008 (0.003-0.032)
Propofol (μg/kg/min)	7 2.1 (0.7-3.8)	15 3.2 (0.3-55.5)
Other	-	4
Fentanyl (μg/kg/min)	95 0.15 (0.08-0.27)	191 0.24 (0.11-0.34) ***
Other analgesics	1	14
Pancuronium (μg/kg/min)	97 0.69 (0.37-1.02)	202 0.58 (0.38-0.94) ***
Vecuronium (μg/kg/min)	13 0.48(0.35-0.58)	2 0.77(0.69-0.86) **

** $p < 0.01$, *** $p < 0.001$

Table 14. Interviews and awareness with recall and mean doses of isoflurane and atracurium during the year of Study 1.

Time period	*Number of patients and percentage of total*				*Dose*	
	Number of interviews	*Awareness group 1*	*Awareness group 2*	*Awareness group 3*	*Isoflurane (Fi%)*	*Atracurium (μg/kg/min)*
Three months preceding the study	-	-	-	-	0.55	7.9
1st quarter of the 12 months	948	5 (0.5%)	3 (0.3%)	1 (0.1%)	0.58	10.5[1)]
2nd quarter of the 12 months	740	1 (0.1%)	3 (0.4%)	2 (0.3%)	0.70[1)]	8.6
3rd quarter of the 12 months	452	1 (0.2%)	0	1 (0.2%)	0.68	8.6
4th quarter of the 12 months	471	2 (0.4%)	0	0	0.73[1)]	8.7
Total	2611[2)]	9 (0.3%)	6 (0.2%)	4 (0.2%)		

[1)] $p<0.05$ vs. the three month period preceding the study.

[2)] Total number of interviews was 2612. We were unable to locate the operation day of one patient, as the matching social security number could not be found in the hospital computer files.

Table 15. The patient claims filed because of awareness during general anesthesia, and the compensations granted.

Age (yrs)	*Sex (m/f)*	*Experience*	*Operation*	*Compensation (FIM)*
53	m	Details of a thoracotomy operation, pain.	Thoracotomy	4,000
27	m	Intubation, operation details, pain	Appendectomy	9,600
41	f	Pain, impossibility to move.	Evacuation of abdominal hematoma	5,000
36	f	Pain, inability to move.	Laparoscopic sterilization	7,000
37	f	Pain, heard discussions.	Tonsillectomy	4,500
40	m	Pain, inability to signal awareness	Thoracotomy	None
45	m	Accidental extubation followed by reintubation using long-acting muscle relaxants. After that inability to move, shortness of breath while on ventilator without anesthesia or sedation, extreme anxiety	Post-op treatment in the recovery room after resuturation of a laparotomy wound	None
25	f	Intubation, insertion of operative instruments, pain	Laparoscopic cholecystectomy	None
47	f	Inability to move or breath	Excision of a mammary gland and axillary lymph nodes	4,500
26	f	Feeling of paralysis, tracheal tube in the throat, insertion of operative instruments, pain, heard discussions	Laparoscopic cholecystectomy	8,000
56	f	Pain, inability to signal awareness and pain	Incision of a foot abscess	5,000

the compensation granted, if any, is shown in Table 15. The mean age of the 11 cases was 39.4 years; four patients were male and seven female. The mean compensation paid was FIM 4,327 (EUR 727), or FIM 5,950 (EUR 1,001) if the patients who were not compensated are excluded. The compensation was technically granted because of pain.

6. Discussion

6.1. Patients' experiences during the episode of intra-anesthetic awareness

Seventy patients with awareness during general anesthesia were analyzed in the present thesis. Tactile perceptions (recalled by 64 % of patients) were the most common sensory modality during the episode of awareness. This was followed by pain (32 %) and visual recollections (18 %) (Table 7). Paralysis was recalled by 80 % of the thirty patients who responded to this question. These figures are similar to those reported previously (Moerman *et al.*, 1993; Schwender *et al.*, 1998; Sandin *et al.*, 2000). Lower incidence of painful awareness or sensory perceptions have also been reported (Domino *et al.*, 1999). However, based on the present thesis and other recent studies (Sandin, and Nordström, 1993; Nordström *et al.*, 1997; Sandin *et al.*, 2000) the incidence of painful awareness is likely to be higher than previously suggested (Jones, 1994). The majority (83 %) of patients understood immediately that they are aware of the operation and did not consider their situation as a dream or hallucination. Immediate anxiety over what is going on was felt by 62 % of the patients but, perhaps astonishingly, only 17 % of the patients with awareness considered the episode of awareness as the worst perioperative experience in the early post-operative interview.

6.2. Methods used in the present studies

6.2.1. Interviews

Structured post-operative interview was used in Studies 1-3 to detect patients with awareness and recall. Interviews are obviously the only currently available method to find out experiences and recollections of another person. However, the results of an interview, if negative, always leave some doubt (Kihlstrom, and Schacter, 1990). The results of an interview are not always easy to interpret, and the contents of a post-operative interview range from no memories through vague, dream-like recollections to exact verbatim descriptions of the occurrences in the operating room. However, the patient's interpretation of his or her memories is of importance, and consequently, if the patient interprets a vague memory meaning intraoperative awareness, mental after-effects may follow. To complicate things further, it has been shown that recollections immediately after a very traumatizing incident contain little or no narrative component, and the patient may react to the post-operative interview only with crying, for example (Van Der Kolk, and Osterman, 2000). It has also been shown by Sandin and co-workers that more than one interview several weeks apart is needed as new cases of patients with awareness and recall could be found in each interview (Sandin *et al.*, 2000). All these problems accompanied by the low incidence of awareness, and consequently, large samples needed, make the interviews both laborious and time-consuming.

In Study 1, interviews were performed by PACU nurses. Two problems arose from this arrangement: first, a large number of patients were not interviewed because the nurses were engaged in other activities, and second, some cases suggestive of awareness and recall were not always immediately identified but were noted only after screening of interview sheets by the investigators. The problem of low interview-rates is not rare in large interview studies (Kapur, 1994), and the investigators were convinced that the sample in the Study 1 was representative of the whole surgical population. The second problem prevented the recruitment all possible cases of awareness, which were eventually found, to the psychiatric interviews. This was a major draw-back since we were not able to describe the pattern of possible psychiatric after-effects in a prospective manner.

Still another problem is that very sick patients that were treated in the ICU were excluded form the study. It may be that these patients do not receive as much anesthetic as other patients because of the severity of their disease. Therefore, they may be predisposed to awareness. On the other hand, interviewing these patients after the ICU is difficult, because the ICU period itself likely produces confusing recollections (Aitkenhead, 1989; Fu-Jin *et al.*, 1997).

As usual during the time of the studies, only one screening interview was used in Studies 1-3 and, therefore, we probably did not identify all cases of awareness and recall.

6.2.2. Anesthetic records

Manual anesthetic charts were used for calculating the anesthetic drug doses (Studies 1-3) and values of the measured physiologic variables (Study 4). It has been shown in many studies that manual anesthetic charts tend to include errors, particularly in the measured variables (Junger *et al.*, 1999; Sado, 1999). It is, therefore, likely that using computer based data would have been superior to manual records. However, computerized charting was not available at the time of these studies.

Some of the cases with awareness and recall in Study 4 dated from the 1970s. There may be systematic changes in the practice of anesthesiology between those days and the 1990s when the control patients' data were recorded. However, the study concentrated on physiologic reactions to intraoperative awareness which are not likely to change over this time span. Furthermore, there were no differences in anticholinergic or sympathomimetic drug dosing between the patients with and without awareness, and the median date of general anesthesia for the patients studied was 1994. Therefore, it is unlikely that the time of the anesthesia during which awareness occurred would have had large effect on the study.

6.3. Incidence of awareness with recall during general surgery

In Study 1, an overall incidence of awareness with recall during general anesthesia was found to be 0.73 % (Table 8). The incidence of awareness when counting only patients with some form of objective memories was 0.38 %. However, even these cases included many which probably would not be considered to represent awareness during general anesthesia, as they include patients recalling extubation (Patients # 2, 9, 11, 16, 19 in Appendix). If all these patients are dropped, we are left with an incidence of 0.19 %.

Certain difficulties exist in comparing incidence figures of awareness with recall during general anesthesia between different studies. Firstly, to evaluate recall, one needs to rely on the story of the patient. In terms of objective, verifiable facts recalled, different grades of memories exist, and consequently, classifying patients' memories becomes more or less subjective and obscure. Secondly, authors of the studies define the time of wakeup from general anesthesia differently. Some feel that extubation or residual relaxation and associated breathing difficulties are not awareness during anesthesia. We did include these cases, because from a patient's point of view, there is often no difference between the intraoperative and the immediate postoperative periods (Ho, 2001). Thirdly, very sick patients often are excluded from the studies, many times for practical reasons. These patients are cared for in the ICU, postoperative ventilator therapy and sedation may be needed for variable lengths of time. All this poses considerable difficulties for the postoperative interviews. Furthermore, the sickest patients may receive less anesthetics than other patients, and therefore, may be prone to awareness during anesthesia. Fourthly, the methodology of assessing awareness and recall varies between studies: structured interview is the most popular method, but non-structured interviews and interviews during hypnosis also have been used. Fifthly, the timing and number of interviews used to detect awareness vary between studies.

In Study 1, the incidence of clear, intraoperative, long-lasting awareness (Grade 3) was 0.15 %. This is very similar to the incidence reported by the most recent large study, which reported an incidence of 0.16 % (Sandin *et al.*, 2000). The criteria behind these figures seem to be somewhat similar, although the 19 patients reported in the study by Sandin and co-workers were further classified into definite, probable, and possible categories. These incidence figures are also of the same order of magnitude as those published by Liu *et al.* in 1991 (0.2 %). Earlier large studies have usually reported slightly higher incidences (Table 2).

Sandin and co-workers interviewed their patients three times, and found that only six of 18 patients recalled awareness in the first interview in the PACU, 12/18 patients recalled awareness in the second interview 1-3 days after anesthesia, and 17/18 in the third interview 7-14 days after anesthesia. Based on these figures it is likely that in the present Study 1 (patients interviewed in the PACU only), and in the studies by Liu *et al.* (one interview 20-36 hours postoperatively) and by Pedersen and Johansen (1989) (one interview on first postoperative day), the observed incidence of awareness underestimates the true incidence. It seems, therefore, that the incidence of awareness and recall is declining.

In the present Study 1, there were five patients (0.2 %) with recollections related to unpleasant extubation or breathing difficulties on awakening. Some of these patients may be in danger of developing post-operative psychiatric complications similar to those with definite intraoperative awareness.

6.4. Incidence of awareness with recall during cardiac surgery

In Study 2, we report an incidence of awareness of 4 % in 1992, and 1.5 % in 1993. In this study, grading of memories was not used but all of the reported patients recollected memories likely of intraoperative origin. Later, one patient (Patient # 24 in Appendix) in the second half of Study 2, was considered a short-lasting case of awareness and graduated to Group 2.

In Study 3, an overall incidence of awareness with recall during general anesthesia was found to be 2.3 % (Table 9). These patients almost certainly include some whose memories originate in the ICU while patients themselves interpret the memories as intraoperative. The incidence of awareness when counting only patients with some form of objective memories was 0.54 %. In this case too, there were two patients (Patients # 28 and 29 in Appendix) with memories probably originating during transport from angioplasty into an emergency CABG operation (# 28) and from ICU to the operating room for emergency re-sternotomy because of bleeding (# 29). If these patients are omitted, the incidence of patients with likely intraoperative awareness was 0.3 %.

Interpreting the results of studies on awareness during cardiac anesthesia is influenced by the same factors as the studies on general surgery. In addition, all patients are treated in the ICU for a variable period of time and patients' interpretation of their recollections can be different from the interpretation of the hospital or study personnel. The longer the postoperative intensive care lasts, the more complicated matters become. We have therefore decided not to include patients with postoperative ICU stay over five days.

The incidence found in Study 3 is similar to that found by Dowd *et al.* (1998) (0.3 %) if only likely cases of true intraoperative awareness are counted. It also seems that incidence of awareness during cardiac surgery has diminished over the years and is of similar order of magnitude, or only slightly higher, than during general surgery (Table 3).

6.5. Differences in anesthetic drug dosing between patients with and without awareness

There are few other studies (Phillips *et al.*, 1993) except those presented in this thesis that have compared the doses of primary anesthetic drugs between patients with and without awareness. We noted differences in the dosing of isoflurane and propofol in Study 1, and in the dosing of midazolam during cardiac surgery in Study 3. The mean doses of anesthetics are smaller in patients with awareness, and therefore a major contribution to the existence of this complication is that not enough anesthetics are administered to every patient.

One must interpret the results of Studies 1 and 3 cautiously in this respect. Firstly, the same problems apply as for assessing awareness: if not all patients with awareness are found and if patients without awareness are included in the wrong groups, the results will be biased. Secondly, calculating doses of single anesthetics may not be appropriate as general anesthesia is not usually the result of a single drug but a combination of drugs. Therefore, one should be able to create a summary measure of the anesthetic effect of a combination of i.v. and volatile anesthetics, which is of course, not currently possible. A third problem is that in these studies, awareness and recall are treated as one phenomenon. In reality, we are dealing with two linked phenomena: awareness during general anesthesia, and later recall. It seems that midazolam, and probably all benzodiazepines, induce profound amnesia but, based on the studies using IFT, not unconsciousness (Russell, 1993).

6.6. Conventional statistical methods and artificial neural networks in detecting awareness from monitored physiologic parameters

The conclusion from the literature is that standard physiologic monitoring is not helpful in detecting awareness during general anesthesia. In current anesthesiology practice, however, physiologic monitoring of heart rate, blood pressure, arterial blood oxygen saturation, and ventilatory gas composition comprise the standard monitoring (Rosenberg *et al.*, 1992). Neurophysiologic monitoring, even if becoming increasingly common, is much less often used. Even the current Nordic standards suggest that "state of consciousness should be clinically observed" (Rosenberg *et al.*, 1992). The concept of following "clinical signs" in monitoring consciousness is also constantly brought to consideration when discussing awareness during general anesthesia (Gilston, 2000).

Artificial neural models have worked well in detecting complex combination patterns in imaging, waveform analysis, and diagnostics (Baxt, 1995). We therefore wanted to study the feasibility of this type of artificial intelligence in the analysis of data obtained from standard physiologic monitors. For a comparison, conventional statistical methods (Poisson regression) were used as well. The best neural models, picked by the likelihood ratio, had a high specificity (98 %) but a low sensitivity (23 %). In the Poisson regression analysis, patients with awareness had higher blood pressures and heart rates than patients without awareness. Together these findings seem to imply that some patients react to awareness by change of autonomic monitored parameters, and that these patients can be picked by the artificial neural model, while no pattern of constant in the group of patients with awareness emerges that can be used to detect them as a group. This further confirms that monitoring of heart rate, blood pressure, and other standard variables is not valuable in monitoring consciousness. However, awareness must be considered as one possible explanation for a tachycardia or high blood pressure during general anesthesia.

Our studies are limited by the fact that we were unable to retrospectively pinpoint the exact time of inadequate anesthesia in the patients who reported recall. Therefore, we had to use statistical summary functions, such as mean, minimum and maximum, of the actual data. If one knew the timing of awareness, actual values measured during that time could be used for training the neural network models. This could increase the information value of the data. Furthermore, manual data records were used in these studies, as not many computerized records of patients with awareness and recall were available to us. Manual records contain errors; for example, true measured highest and lowest values tend to be missing in manual recordings (Edsall *et al.*, 1993).

6.7. The possibility of reducing the incidence of awareness by giving feedback information to the anesthesiologists

Education of practitioners in the field of anesthesiology is a way to try to reduce awareness during general anesthesia (Ghoneim, 2001). We had noticed a fairly high incidence of awareness during cardiac anesthesia in our unit in 1992. Therefore, information about this anesthesia complication and about its avoidance was increased in the education files of the unit. We also decided to estimate the effect of this increased information and repeated the structured interview in 1993 (Study 2).

Incidence of awareness decreased from 4 % to 1.5 % between the study periods, and the relative risk for awareness in 1992 was 275 % (95 % CI 63-1204 %) of the risk in 1993 in our unit. Simultaneously, the use constant infusion of anesthetics or constant use of a volatile anesthetics increased, consumption of primary anesthetic agents increased and consumption pancuronium (the primary muscle relaxant used in cardiac anesthesia at that time) decreased, all changes proposed in the educational materials.

The change in the incidence of awareness between the years 1992 and 1993 is not statistically significant. However, there seems to be a decreasing trend in awareness during cardiac surgery starting in 1992 (Table 9). It seems likely that informing the anesthesiologists about the possibility of awareness and recall during cardiac anesthesia is one reason for the decreasing incidence of this complication.

There are always many reasons for the change of behavior in anesthesiologists, as well as other human beings. Therefore, we cannot be sure that changes in the use of anesthetic drugs and concurrent decrease in the incidence of awareness were due to the information given to the anesthesiologists. However, there are no other obvious explanations for the change in practice during that particular time. Our study seems to put forth further evidence in favor of the value of education in reducing awareness during anesthesia.

These findings are further supported by findings during anesthesia for general surgery in Study 1. In this study, the anesthesiologists were informed about the nature of the study but no specific suggestions were given. The mean dosing of isoflurane increased during the study compared to the three-month period immediately preceding the study. Simultaneously, a decreasing trend in the incidence of awareness was noted, which, however, was not statistically significant at the 95 % level. The anesthesiologists likely changed their way of anesthetizing patients because they knew they were being observed in conjunction with an ongoing study.

Another possible conclusion drawn from these two studies may be that the studies themselves and not the information changed the behavior of the anesthesiologists. The effect of the measurement procedure on the measured variable (Hawthorne effect) is an inherent cause of bias in all empirical studies. It is very difficult to try to eliminate the Hawthorne effect by blinding the anesthesiologists to a large ongoing interview study. A possibility to quantify this bias might be estimating anesthetic drug dosing before, during, and *after* a study of this kind.

6.8. Psychiatric consequences of awareness during anesthesia

There is one recent small prospective study on the incidence of psychiatric complications after awareness with recall during general anesthesia. In this study, 22 % of patients with previous awareness and recall had PTSD after a median of 20 months. The incidence of PTSD may be even higher because the investigators state that they have reasons to believe that the unwillingness of some patients to participate in the study constituted avoidance behavior, a typical symptom of PTSD. Furthermore, 11 % of the patients with previous awareness experienced some symptoms of PTSD in the follow-up, although they did not fulfill all criteria of PTSD (Lennmarken *et al.*, 2002).

The studies that have used some form of advertising, or complication databases, to gather patients who have suffered from awareness during anesthesia, tend to have a high number of patients suffering PTSD, or other serious psychiatric after-effects (Cobcroft, and Forsdick, 1993; Moerman *et al.*, 1993; Schwender *et al.*, 1998; Domino *et al.*, 1999). In addition, it is likely that the most severely traumatized patients are not likely to be able to respond to the advertisements, and control groups are lacking in these studies (Wang, 2001).

In the study by Bergström and Bernstein, the incidence of psychiatric after-effects was very high: four out of six patients were suffering from after-effects a year after the anesthesia, and one was in psychiatric care (Bergström, and Bernstein, 1968). In this study, all patients anesthetized by two different methods were followed.

We found that none of the five patients with awareness (Study 1), who were recruited for psychiatric interview and testing, developed any serious after-effects. One patient had intense fear that subsided spontaneously. Three of the five patients had suffered from depression in the past, and one of the three needed antidepressant medication after the awareness period. It seems that the experiences recalled by these patients were not very traumatizing and that serious psychiatric after-effects are not very common. On the other hand, none of the control patients in our Study 1 had any psychiatric after-effects. Therefore, even if serious psychiatric after-effects of awareness are unlikely, sequelae of some sort may be much more common.

The number of patients included in the psychiatric interviews and testing, is however quite small, which makes definite conclusions impossible. We were not able to recruit all patients with possible awareness into the psychiatric interview and testing because these patients were only found in the retrospective scrutiny of the interview records. It has also been shown that very traumatic memories tend to be primarily implicit memories with sensorimotor or affective nature but little narrative component. Patients with traumatizing memories are able to speak coherently about their traumatic recollections only after variable time span (Van Der Kolk, and Osterman, 2000). Therefore, it is possible that severely traumatized patients are missed in the present Study 1. This has also been found to be the case as patients may initially seem to be doing well after an awareness episode, but later do develop psychiatric problems (Lennmarken *et al.*, 2002).

In conclusion, we do not know the current incidence of psychiatric after effects of intraoperative awareness. It is likely that the incidence of severe psychiatric consequences is relatively high (probably 20-30 %), but also, that some patients will not develop any psychiatric after-effects. The scope of psychiatric after-effects ranges from nil to very traumatizing PTSD that may completely ruin the life of the patient for many years. Information about this possibility should probably be given to surgeons and primary care physicians who are more likely than anesthesiologists to meet the patient when the problems become manifest.

6.9. Medico-legal consequences of awareness with recall in Finland

To my knowledge, there have been no cases of litigation and trial resulting from intraoperative awareness in Finland. The Patient Injury Act, effective since May 1, 1987 in Finland, states that compensation for patient injury is payable after injury from medical treatment. The PIA handles all the claims, makes the decisions and pays the compensations. The basic principle of the no fault scheme is that the patient does not sue through the courts, but submits an insurance claim which will bring compensation if the insurers are satisfied that the injury was caused by the treatment. Consideration will, however, be given to unavoidable consequences of therapy and to necessary risk-taking by health care providers. This insurance scheme allows patients to be compensated for injuries arising from medical treatment without the need to prove fault and causation through adversarial litigation.

In Study 5, we studied insurance claims submitted to PIA between May 1, 1987 and December 31, 1993. Four claims because of awareness during general anesthesia had been filed representing one insurance claim for about 350,000 general anesthetics. During the same time period, 391 claims had been filed for anesthesia care, giving for awareness during general anesthesia a 1 % share of claims against the anesthetic practice.

Between January 1, 1994 and June 15, 1997 another seven insurance claims resulting from anesthetic awareness were filed (Study 4). One insurance claim every twenty months was filed from 1987 to 1993, and one every six months from 1994 to 1997. Compensation was granted in 73 % of the cases; the average award was EUR 1,001.

Of the 4,183 claims in the ASA Closed Claims Project database (Domino *et al.*, 1999) 79 (1.9 %) were filed because of awareness during anesthesia. Compensations ranged from USD 1,000 to 600,000. High compensation (GBP 13,000) for awareness during anesthesia has also been reported in the U.K (Domino, and Aitkenhead, 2001).

In conclusion, the medicolegal consequences of awareness during general anesthesia in Finland have been relatively rare, although there may be a slightly increasing trend. Compensations granted for pain and awareness during anesthesia have been small according to the policy of the PIA to keep compensations for immaterial loss low.

7. Conclusions

1. The incidence of awareness during general anesthesia for general surgery seems to be in slow, constant decline. The current incidence of undisputed intraoperative awareness is about 0.1-0.2 % of all general anesthetics. If cases of unpleasant awakening are counted, the incidence is about 0.4 %, and if cases with possible awareness are included, the incidence is 0.7 %.

2. The incidence of awareness during anesthesia for cardiac surgery is also in decline. Current estimate of the incidence of undisputed intraoperative awareness is 0.3 % of all cases of cardiac anesthesia. If all possible cases of awareness are counted, the incidence is 2.3 %. Incidence of awareness during cardiac surgery was previously much higher than during general surgery but it has come down to a level almost similar to the incidence during general surgery.

3. Lower doses of anesthetics were used for patients with awareness than for those without, during anesthesia for general surgery: isoflurane 0.42 Fi% vs. 0.65 Fi% and propofol 73 µg/kg/min vs. 228 µg/kg/min, respectively (Study 1).
   Lower dose of midazolam was used during cardiac surgery: 0.8 µg/kg/min vs. 1.1 µg/kg/min (Study 3).
   A principal factor for the existing measurable incidence of awareness during anesthesia is the use of an insufficient concentration of anesthetic for the patient's need.

4. Standard physiologic monitoring is not reliable for monitoring consciousness during general anesthesia. Even with computer-based artificial intelligence, it is currently not possible to create systems able to reliably distinguish between patients with and without awareness. However, patients with awareness as a group tend to have higher blood pressure and heart rate than patients without awareness.

5. Information about awareness during general anesthesia, and means of preventing it lead to a lowering trend of its incidence. Concurrently, there was increase in the consumption of primary anesthetics and decrease in the consumption of pancuronium during cardiac surgery. All these changes were suggested in the information given. It is likely that information given to anesthesiologists leads into a change in their practice of anesthetizing patients.

6. Psychiatric after-effects of awareness during general anesthesia range from no effects to invalidating chronic PTSD. Current incidence of serious psychiatric after-effects is not known, but it is likely

that a significant number (possibly 20-30 %) of patients suffer from serious psychiatric consequences.

7. Awareness during general anesthesia has triggered a small number of Patient Insurance claims in Finland (about 1 % of anesthesia-related claims). Seventy percent of the patients who have submitted insurance claims have received compensations for pain, the mean amount of compensation being EUR 1,000.

8. Practical considerations

A practical goal for an anesthesiologist is a safe general anesthesia without awareness and, certainly, without post-operative recall. There is currently no evidence that any kind of premedication, or withholding premedication for that matter, would affect the incidence of awareness and recall. Therefore, the choice of premedication should be based on other considerations of patient safety, comfort, and requirements of surgery. There is currently no consensus on whether the patients should be forewarned about the possibility of awareness during general anesthesia. Some have, however, suggested that this might give the patient better chances of coping with possible awareness and that mental after-effects would be more unlikely (Holt, and Yate, 1993). Certainly, discussing this matter is wise if the anesthesiologist foresees a need for very light anesthesia for some reason.

General anesthesia may be induced with any inhaled or i.v. anesthetic drugs. The dose of the chosen drug should be large enough to cover the stimulus of possible endotracheal intubation. If prolonged laryngoscopy is required, one should not forget to maintain general anesthesia with supplemental doses of the induction agent or with a potent inhalational anesthetic. During the operation, anesthesia should be maintained with continuous administration of an anesthetic, whether that be i.v. or inhaled. Anesthetics should be administered in such amounts that unconsciousness is maintained until the patient's trachea is extubated and muscle strength has recovered to sufficient amount to sustain normal breathing. A technique relying on N_2O, whether supplemented with an opioid or not, to maintain general anesthesia, is not acceptable. There is some evidence that desflurane, isoflurane, and sevoflurane cause unconsciousness and amnesia in lower concentration relative to their $MAC_{\text{skin incision}}$ than halothane (Eger, 2001). Therefore, the use of these inhaled anesthetics would be wise if hemodynamic instability is encountered. The maintenance of anesthesia with large doses of benzodiazepines, with or without opioid supplementation, would probably cause amnesia but not unconsciousness. Therefore, this technique is not as good as using potent inhaled or i.v. general anesthetics. However, there is currently no evidence that awareness without later recall is detrimental to the patient, and in critical hemodynamic situation using benzodiazepines instead of general anesthetics may be acceptable. NMBs should be used as sparingly as possible unless indicated for surgery or intubation.

There is currently no evidence that awareness and recall could be prevented by monitoring consciousness with sophisticated methods, such as AEP or BIS. However, any clinical signs are much more unreliable in this respect and, certainly, it would be wise to use EEG-based monitoring if a patient has a history of awareness and recall under anesthesia. Some of these patients have abnormal pharmacokinetic or –dynamic profiles, and monitoring the effect of the anesthetic drugs on the effector site (brain) should be used.

If a patient after all has suffered form awareness and recalls this postoperatively, psychiatric consultation and follow-up is recommended. Quality control programs, such as postoperative interviews or surveys, should incorporate questions revealing possible cases of intraoperative awareness.

9. Future implications

It seems that prospective, multi-center studies would be needed to establish after-effects of awareness and recall during anesthesia, as well as, the after-effects of awareness, or wakefulness, without recall. There is evidence, presented in this thesis, too, that awareness and recall may be followed by detrimental after-effects, but less evidence exists about the possibility of negative after-effects after wakefulness without later recall. An associated question is the effect of drugs that have effect on memory but are not likely to be anesthetics in the sense of being able to suppress consciousness and prevent wakefulness during general anesthesia. Benzodiazepines are the most notorious example of such drugs. These drugs are also often used as component of modern general anesthesia.

The question of monitoring consciousness during general anesthesia is also important. Monitoring the central nervous system function with currently available methods is fairly expensive. It is suggested, but not shown, that awareness and recall may be prevented by these modes of monitoring (Kelly *et al.*, 2000). A particular problem of all the methods (BIS and AEP) available today is that they are retrospective in the sense that the result displayed by the monitoring systems represents time 10-30 seconds past the present. If the patient is conscious at the present time, it will only be displayed a minute later (Rosow, and Manberg, 1998). It is not established, whether actions taken a few minutes after the occurrence of consciousness during general anesthesia are able to prevent all negative after-effects.

The problem of all studies on awareness with and without recall is the large amount of patients needed (O'Connor *et al.*, 2001). Multi-center studies are obviously necessary to overcome these problems. In addition, the amount of labor needed, for example, to show a 50 % fall in the incidence of awareness and recall from the current level using a hypothetical new technique, would require three to five years of labor only to complete the structured interviews. Even though we are dealing with a very basic dilemma of anesthesiology – consciousness – it is questionable whether or not such an investment of time and money would be worthwhile.

There are no studies on the incidence of awareness and recall in children. The general anesthetics during childhood, however, may be somewhat different from that used in adults. The fact that the ability to conduct structured interviews diminishes as the age of the target group decreases, makes collection of accurate data in children with current methodology difficult if not impossible. A technique suitable for evaluating awareness and recall in children would be most welcome.

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References

Anonymous. Awareness during anaesthesia. *BMJ* 1: 977, 1976.

Anonymous. Awareness in general anaesthesia. *BMJ* 280: 811, 1980.

Anonymous. *Webster's encyclopedic unabridged dictionary of the English language*. New York: Portland House, 1989.

Anonymous. *NNModel32 Version 1.0 User's manual.* New York, NY: Neural Fusion, 1998.

Anonymous. Precedents of the Finnish Supreme Court. *http://www.finlex.fi/oikeus/index.html.* Accessed: 4.1.2002.

Abouleish E, Taylor FH. Effect of morphine-diazepam on signs of anesthesia, awareness, and dreams of patients under N2O for cesarean section. *Anesth Analg* 55: 702-5, 1976.

Agarwal G, Sikh SS. Awareness during anaesthesia. A prospective study. *Br J Anaesth* 49: 835-8, 1977.

Aitkenhead AR. Analgesia and sedation in intensive care. *Br J Anaesth* 63: 196-206, 1989.

Aitkenhead AR. Awareness during anaesthesia: what should the patient be told? *Anaesthesia* 45: 351-2, 1990.

Aldrete JA, Wright AJ. Concerning the acceptability of awareness during surgery. *Anesthesiology* 63: 460-1, 1985.

Altman DG. *Practical statistcs for medical research*. London: Chapman & Hall, 1991.

Andrade J, Baddeley A. Human memory and anesthesia. *Int Anesth Clin* 31: 39-51, 1993.

Baddeley A. *Human memory, theory and practice*. Hove: Lawrence Erlbaum Associates, 1990.

Bailey AR, Jones JG. Patients' memories of events during general anaesthesia. *Anaesthesia* 52: 460-76, 1997.

Baraka A, Louis F, Noueihid R, Diab M, Dabbous A, Sibai A. Awareness following different techniques of general anaesthesia for caesarean section. *Br J Anaesth* 62: 645-8, 1989.

Barr AM, Wong RM. Awareness during general anaesthesia for bronchoscopy and laryngoscopy using the apnoeic oxygenation technique. *Br J Anaesth* 45: 894-900, 1973.

Baxt WG. Application of artificial neural networks to clinical medicine. *Lancet* 346: 1135-8, 1995.

Bennett H. Response to intraoperative converation, in response. *Br J Anaesth* 58: 134-5, 1986.

Bergström H, Bernstein K. Psychic reactions after analgesia with nitrous oxide for caesarean section. *Lancet* 2: 541-2, 1968.

Blacher RS. On awakening paralyzed during surgery. A syndrome of traumatic neurosis. *JAMA* 234: 67-8, 1975.

Blacher RS. Awareness during surgery. *Anesthesiology* 61: 1-2, 1984.

Bogetz MS, Katz JA. Recall of surgery for major trauma. *Anesthesiology* 61: 6-9, 1984.

Bogod DG. Detecting awareness during general anaesthesia. *Anaesthesia* 45: 590, 1990.

Bogod DG, Orton JK, Yau HM, Oh TE. Detecting awareness during general anaesthetic caesarean section. An evaluation of two methods. *Anaesthesia* 45: 279-84, 1990.

Breckenridge J, Aitkenhead AR. Isolated forearm technique for detection of wakefulness during general anaesthesia. *Br J Anaesth* 52: 665P, 1981.

Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. *Br J Anaesth* 42: 535-42, 1970.

Browne RA, Catton DV. A study of awareness during anesthesia. *Anesth Analg* 52: 128-32, 1973a.

Browne RA, Catton DV. Awareness during anaesthesia: A comparison of anaesthesia with nitrous oxide – oxygen and nitrous oxide – oxygen with Innovar®. *Canad Anaesth Soc J* 20: 763-8, 1973b.

Chortkoff BS, Bennett HL, Eger EII. Does nitrous oxide antagonize isoflurane-induced suppression of learning? *Anesthesiology* 79: 724-32, 1993.

Chortkoff BS, Eger EII, Crankshaw DP, Gonsowski CT, Dutton RC, Ionescu P. Concentrations of desflurane and propofol that suppress response to command in humans. *Anesth Analg* 81: 737-43, 1995.

Clark DL, Rosner BS. Neurophysiologic effects of general anesthetics: I . The electroencephalogram and sensory evoked responses in man. *Anesthesiology* 38: 564-82, 1973.

Cobcroft MD, Forsdick C. Awareness under anaesthesia: the patients' point of view. *Anaesth Intensive Care* 21: 837-43, 1993.

Cormack RS. Conscious levels during anaesthesia. *Br J Anaesth* 71: 469-71, 1993.

Crawford JS. Awareness during operative obstetrics under general anaesthesia. *Br J Anaesth* 43: 179-82, 1971.

Crawford JS, Lewis M, Davies P. Maternal and neonatal responses related to the volatile agent used to maintain anaesthesia at caesarean section. *Br J Anaesth* 57: 482-7, 1985.

Crawford JS. Fetal well-being and maternal awareness. *Br J Anaesth* 61: 247-9, 1988.

Critchley M. Butterworths Medical Dictionary (2 ed.). London: Butterworth & Co (Publishers) Ltd, 1978, p. 1942.

Cross SS, Harrison RF, Kennedy RL. Introduction to neural networks. *Lancet* 346: 1075-9, 1995.

Cundy JM. Post traumatic stress disorders. *Br J Anaesth* 75: 501-2, 1995.

Cundy JM, Dasey N. An audit of stress disorders related to anaesthesia. In: *Memory and awareness in anaesthesia III*, Bonke B, Bovill JG, Moerman N, eds. Assen: Van Gorcum, 1996: 143-50.

Degoratis LR, Lipman RS, Covi L. An out-patient rating scale: preliminary report. *Psychophramacol Bull* 9: 13-28, 1973.

Desiderio DP, Thorne AC. Awareness and general anaesthesia. *Acta Anaesthesiol Scand Suppl* 92: 48-50, 1990.

Domino KB, Posner KL, Caplan RA, Cheney FW. Awareness during anesthesia: a closed claims analysis. *Anesthesiology* 90: 1053-61, 1999.

Domino KB, Aitkenhead AR. Medicolegal consequences of awareness during anesthesia. In: *Awareness during anesthesia*, Ghoneim MM, ed. Oxford: Butterworth-Heinemann, 2001: 155-72.

Dowd NP, Cheng DC, Karski JM, Wong DT, Munro JAC, Sandler AN. Intraoperative awareness in fast-track cardiac anesthesia. *Anesthesiology* 89: 1068-73, 1998.

Drummond JC. Monitoring depth of anesthesia: with emphasis on the application of the bispectral index and the middle latency auditory evoked response to the prevention of recall. *Anesthesiology* 93: 876-82, 2000.

Dutton RC, Smith WD, Smith NT. Wakeful response to command indicates memory potential during emergence from general anesthesia. *J Clin Monit* 11: 35-40, 1995.

Dwyer R, Bennett HL, Eger EId, Heilbron D. Effects of isoflurane and nitrous oxide in subanesthetic concentrations on memory and responsiveness in volunteers. *Anesthesiology* 77: 888-98, 1992.

Edsall DW, Deshane P, Giles C, Dick D, Sloan B, Farrow J. Computerized patient anesthesia records: less time and better quality than manually produced anesthesia records. *J Clin Anesth* 5: 275-83, 1993.

Eger EI, Saidman LJ, Brandstater B. Minimum alveolar concentration: A standard of anesthetic potency. *Anesthesiology* 26: 756-63, 1965.

Eger EI. Does 1 + 1 = 2? *Anesth Analg* 68: 551-2, 1989.

Eger EI. Age, minimum alveolar anesthetic concentration, and minimum alveolar anesthetic concentration-awake. *Anesth Analg* 93: 947-53, 2001.

Eger EI. A brief history of the origin of minimum alveolar concentration (MAC). *Anesthesiology* 96: 238-9, 2002.

Evans JM, Davies WL. Monitoring anaesthesia. *Clin Anasthesiol* 2: 243-62, 1984.

Farnsworth GM. Enflurane and the incidence of awareness in Caesarean section. *Anaesthesia* 33: 553, 1978.

Fu-Jin S, Shu-Hsun C, Po-Jui Y, Wen-Yu H, Guey-Shiun H. Turning points of recovery from cardiac surgery during the intensive care unit transition. *Heart Lung* 26: 99-108, 1997.

Galinkin JL, Janiszewski D, Young CJ, Klafta JM, Klock PA, Coalson DW, Apfelbaum JL, Zacny JP. Subjective, psychomotor, cognitive, and analgesic effects of subanesthetic concentrations of sevoflurane and nitrous oxide. *Anesthesiology* 87: 1082-8, 1997.

Ghoneim MM, Mewaldt SP. Benzodiazepines and human memory: a review. *Anesthesiology* 72: 926-38, 1990.

Ghoneim MM, Block RI. Learning and consciousness during general anesthesia. *Anesthesiology* 76: 279-305, 1992.

Ghoneim MM, Block RI. Learning and memory during general anesthesia: an update. *Anesthesiology* 87: 387-410, 1997.

Ghoneim MM. Awareness during anesthesia. *Anesthesiology* 92: 597-602, 2000.

Ghoneim MM, Block RI, Dhanaraj VJ, Todd MM, Choi WW, Brown CK. Auditory evoked responses and learning and awareness during general anesthesia. *Acta Anaesthesiol Scand* 44: 133-43, 2000.

Ghoneim MM. Awareness during anesthesia. In: *Awareness during anesthesia*, Ghoneim MM, ed. Oxford: Butterworth-Heinemann, 2001: 1-22.

Gilston A. Awareness during anaesthesia. *Lancet* 355: 1722, 2000.

Goldmann L, Shah MV, Hebden MW. Memory of cardiac anaesthesia. Psychological sequelae in cardiac patients of intra-operative suggestion and operating room conversation. *Anaesthesia* 42: 596-603, 1987.

Gonsowski CT, Chortkoff BS, Eger EII, Bennett HL, Weiskopf RB. Subanesthetic concentrations of desflurane and isoflurane suppress explicit and implicit learning. *Anesth Analg* 80: 568-72, 1995.

Griffiths D, Jones JG. Awareness and memory in anaesthetized patients. *Br J Anaesth* 65: 603-6, 1990.

Hargrove RL. Awareness under anaesthesia. *J Med Def Union* 9: 9-11, 1987.

Harris TJB, Brice DD, Hetherington RR, Utting JE. Dreaming associated with anaesthesia: the influence of morphine premedication and two volatile adjuvants. *Br J Anaesth* 43: 172-8, 1971.

Haykin SS. *Neural networks: a comprehensive foundation*. Upper Saddle River, New Jersey: Prentice Hall, 1999.

Heier T, Steen PA. Assessment of anaesthesia depth. *Acta Anaesthesiol Scand* 40: 1087-100, 1996.

Hilgenberg JC. Intraoperative awareness during high-dose fentanyl-oxygen anesthesia. *Anesthesiology* 54: 341-3, 1981.

Ho AM. 'Awareness' and 'recall' during emergence from general anaesthesia. *Eur J Anaesthesiol* 18: 623-5, 2001.

Holt GM, Yate PM. Psychological responses to anaesthesia. In: *Hazards and complications of anaesthesia* (2. ed.), Taylor TH, Major E, eds. Edinburgh: Churchill Livingstone, 1993: 447-57.

Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. *Psychosomatic Medicine* 41: 3, 1979.

Hug CC. Does opioid "anesthesia" exist? *Anesthesiology* 73: 1-4, 1990.

Hutchinson R. Awareness during surgery. *Br J Anaesth* 33: 463-9, 1960.

James MFM. Conscious levels during anaesthesia. *Br J Anaesth* 72: 496, 1994.

Jelicic M, Bonke B. The incidence of awareness during anaesthesia. *Anaesthesia* 44: 1004-5, 1989.

Jessop J, Jones JG. Conscious awareness during general anaesthesia-what are we attempting to monitor? *Br J Anaesth* 66: 635-7, 1991.

Jones JG, Konieczko K. Hearing and memory in anaesthetised patients. *BMJ* 292: 1291-3, 1986.

Jones JG. Awareness during general anaesthesia - what are we monitoring. In: *Memory and awareness in anaesthesia IV*, Jordan C, Vaughan DJA, Newton DEF, eds. London: Imperial College Press, 2000: 3-40.

Jordening H, Pedersen T. The incidence of conscious awareness in a general population of anesthetized patients. *Anesthesiology* 75: A1055, 1991.

Junger A, Benson M, Quinzio L, Jost A, Veit C, Klöss T, Hempelmann G. Qualitätsdokumentation mit einem Anästhesie-Informations-Management-System (AIMS). *Anaesthetist* 48: 523-32, 1999.

Kapur PA. Multicenter study versus nausea outcomes: the value of large numbers and the limitations. *Anesth Analg* 78: 5-6, 1994.

Kelly JS, Roy RC. Intraoperative awareness with propofol-oxygen total intravenous anesthesia for microlaryngeal surgery. *Anesthesiology* 77: 207-9, 1992.

Kelly SJ, Myles PS, Bain D, Rosow C, Ramsay J. Case 8-2000. Intraoperative bispectral index monitoring and early extubation after cardiac surgery in patients with a history of awareness under anesthesia. *J Cardiothorac Vasc Anesth* 14: 726-30, 2000.

Kerssens C, Sebel PS. BIS and memory during anesthesia. In: *Awareness during anesthesia* (1. ed.), Ghoneim MM, ed. Oxford: Butterworth-Heinemann, 2001: 103-16.

Kihlstrom JF, Schacter DL. Anaesthesia, amnesia, and the cognitive unconscious. In: *Memory and Awareness in Anaesthesia*, Bonke B, Fitch W, Millar K, eds. Amsterdam: Swets & Zeitlinger Publishers, 1990: 21-44.

Kim CL. Awareness during cardiopulmonary bypass. *AANA-J* 46: 373-83, 1978.

Kochs E, Kalkman CJ, Thornton C, Newton D, Bischoff P, Kuppe H, Abke J, Konecny E, Nahm W, Stockmanns G. Middle latency auditory evoked responses and electroencephalographic derived variables do not predict movement to noxious stimulation during 1 minimum alveolar anesthetic concentration isoflurane/nitrous oxide anesthesia. *Anesth Analg* 88: 1412-7, 1999.

Lennmarken C, Bildfors K, Enlund G, Samuelsson P, Sandin RH. Victims of awareness. *Acta Anaesthesiol Scand* 46: 229-31, 2002.

Liu WH, Thorp TA, Graham SG, Aitkenhead AR. Incidence of awareness with recall during general anaesthesia. *Anaesthesia* 46: 435-7, 1991.

Lubke GH, Kerssens C, Phaf H, Sebel PS. Dependence of explicit and implicit memory on hypnotic state in trauma patients. *Anesthesiology* 90: 670-80, 1999.

Lunn JN, Rosen M. Anaesthetic awareness. *BMJ* 300: 938, 1990.

Lyons G, Macdonald R. Awareness during caesarean section. *Anaesthesia* 46: 62-4, 1991.

Macleod AD, Maycock E. Awareness during anaesthesia and post traumatic stress disorder. *Anaesth Intensive Care* 20: 378-82, 1992.

Mainzer J, Jr. Awareness, muscle relaxants and balanced anaesthesia. *Can Anaesth Soc J* 26: 386-93, 1979.

Mark JB, Greenberg LM. Intraoperative awareness and hypertensive crisis during high-dose fentanyl-diazepam-oxygen anesthesia. *Anesth Analg* 62: 698-700, 1983.

Maunuksela E-L. Hemodynamic response to different anesthetics during open-heart surgery. *Acta Anaesthesiol Scand* Suppl. 65, 1977.

McCleane GJ, Cooper R. The nature of pre-operative anxiety. *Anaesthesia* 45: 153-5 issn: 0003-2409, 1990.

McKenna T, Wilton TNP. Awareness during endotracheal intubation. *Anaesthesia* 28: 599-602, 1973.

Meyer BC, Blacher RS. A traumatic neurotic reaction induced by succinylcholine chloride. *N Y State J Med* 61: 1255-61, 1961.

Miller DR, Blew PG, Martineau RJ, Hull KA. Midazolam and awareness with recall during total intravenous anaesthesia. *Can J Anaesth* 43: 946-53, 1996.

Moerman A, Herregods L, Foubert L, Poelaert J, Jordaens L, L DH, Rolly G. Awareness during anaesthesia for implantable cardioverter defibrillator implantation. Recall of defibrillation shocks. *Anaesthesia* 50: 733-5, 1995.

Moerman N, Bonke B, Oosting J. Awareness and recall during general anesthesia. Facts and feelings. *Anesthesiology* 79: 454-64, 1993.

Moore JK, Seymour AH. Awareness during bronchoscopy. *Ann R Coll Surg Engl* 69: 45-7, 1987.

Mummaneni N, Rao TL, Montoya A. Awareness and recall with high-dose fentanyl-oxygen anesthesia. *Anesth Analg* 59: 948-9, 1980.

Myles PS, Williams DL, Hendrata M, Anderson H, Weeks AM. Patient satisfaction after anaesthesia and surgery: results of a prospective survey of 10 811 patients. *Br J Anaesth* 84: 6-10, 2000.

Newton DEF, Thornton C, Creagh-Barry P, Doré J. Early cortical auditory evoked response in anaesthesia: comparison of the effects of nitrous oxide and isoflurane. *Br J Anaesth* 62: 61-5, 1989.

Ng KH, Gurubatham AI. Awareness during caesarean section under general anaesthesia. *Med J Aust* 2: 774-6, 1974.

Nordström O, Engström S, Persson S, Sandin R. Incidence of awareness in total i.v. anaesthesia based on propofol, alfentanil and neuromuscular blockade. *Acta Anaesthesiol Scand* 41: 978-84, 1997.

O'Connor MF, Daves SM, Tung A, Cook RI, Thisted R, Apfelbaum J. BIS monitoring to prevent awareness during general anesthesia. *Anesthesiology* 94: 520-2, 2001.

Osborne GA, Webb RK, Runciman WB. The Australian Incident Monitoring Study. Patient awareness during anaesthesia: an analysis of 2000 incident reports. *Anaesth Intensive Care* 21: 653-4, 1993.

Osterman JE, van der Kolk BA. Awareness during anesthesia and posttraumatic stress disorder. *Gen Hosp Psychiatry* 20: 274-81, 1998.

Osterman JE, Hopper J, Heran WJ, Keane TM, van der Kolk BA. Awareness under anesthesia and the development of posttraumatic stress disorder. *Gen Hosp Psychiatry* 23: 198-204, 2001.

Parkhouse J. Awareness during surgery. *Postgrad Med J* 36: 674-7, 1960.

Payne JP. Awareness and its medicolegal implications. *Br J Anaesth* 73: 38-45, 1994.

Pedersen T, Johansen SH. Serious morbidity attributable to anaesthesia. Considerations for prevention. *Anaesthesia* 44: 504-8, 1989.

Phillips AA, McLean RF, Devitt JH, Harrington EM. Recall of intraoperative events after general anaesthesia and cardiopulmonary bypass. *Can J Anaesth* 40: 922-6, 1993.

Ponte J. Neuromuscular blockers during general anaesthesia - less may be better. *BMJ* 310: 1218-9, 1995.

Prys-Roberts C. Anaesthesia: A practical or impractical construct? *Br J Anaesth* 59: 1341-45, 1987.

Pöppel E, Schwender D. Temporal mechanisms of consciousness. *Int Anesth Clin* 31: 27-38, 1993.

Quasha AL, Eger EI, Tinker JH. Determination and applications of MAC. *Anesthesiology* 53: 315-34, 1980.

Rampil IJ. Anesthetic potency is not altered after hypothermic spinal cord transection in rats. *Anesthesiology* 80: 606-10, 1994.

Rampil IJ. A primer for EEG signal processing in anesthesia. *Anesthesiology* 89: 980-1002, 1998.

Rosenberg P, Gisvold SE, Flaatten H, Nuutinen L, Stenqvist O, Tryggvason B, Viby-Mogensen J. Guidelines for anaesthesia care in the Nordic countries. *Acta Anaesthesiol Scand* 36: 741-4, 1992.

Rosow C, Manberg PJ. Bispectral index monitoring. *Anesth Clin North Am* 2: 89-107, 1998.

Russell IF. Balanced anesthesia: does it anesthetize? *Anesth Analg* 64: 941-2, 1985.

Russell IF. Comparison of wakefulness with two anaesthetic regimens. Total i.v. v. balanced anaesthesia. *Br J Anaesth* 58: 965-8, 1986.

Russell IF. Midazolam-alfentanil: an anaesthetic? An investigation using the isolated forearm technique. *Br J Anaesth* 70: 42-6, 1993.

Russell IF, Wang M. Absence of memory for intraoperative information during surgery under adequate general anaesthesia. *Br J Anaesth* 78: 3-9, 1997.

Sado AS. Electronic medical record in the intensive care unit. *Crit Care Clin* 15: 499-522, 1999.

Sandin R, Nordström O. Awareness during total i.v. anaesthesia. *Br J Anaesth* 71: 782-7, 1993.

Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. *Lancet* 355: 707-11, 2000.

Saucier N, Walts LF, Moreland JR. Patient awareness during nitrous oxide, oxygen, and halothane anesthesia. *Anesth Analg* 62: 239-40, 1983.

Scheinin H. Lääkkeen pitoisuuden ja vaikutuksen korrelaatio. *Duodecim* 115: 2275-83, 1999.

Schultetus RR, Hill CR, Dharamraj CM, Banner TE, Berman LS. Wakefulness during cesarean section after anesthetic induction with ketamine, thiopental, or ketamine and thiopental combined. *Anesth Analg* 65: 723-8, 1986.

Schwender D, Faber-Zullig E, Klasing S, Poppel E, Peter K. Motor signs of wakefulness during general anaesthesia with propofol, isoflurane and flunitrazepam/fentanyl and midlatency auditory evoked potentials. *Anaesthesia* 49: 476-84, 1994.

Schwender D, Haessler R, Klasing S, Madler C, Pöppel E, Peter K. Mid-latency auditory evoked potentials and circulatory response to loud sounds. *Br J Anaesth* 72: 307-14, 1994.

Schwender D, Kaiser A, Klasing S, Peter K, Poppel E. Midlatency auditory evoked potentials and explicit and implicit memory in patients undergoing cardiac surgery. *Anesthesiology* 80: 493-501, 1994.

Schwender D, Klasing S, Madler C, Pöppel E, Peter K. Midlatency auditory evoked potentials and purposeful movements after thiopentone bolus injection. *Anaesthesia* 49: 99-104, 1994.

Schwender D, Klasing S, Conzen P, Finsterer U, Poppel E, Peter K. Midlatency auditory evoked potentials during anaesthesia with increasing endexpiratory concentrations of desflurane. *Acta Anaesthesiol Scand* 40: 171-6, 1996.

Schwender D, Kunze-Kronawitter H, Dietrich P, Klasing S, Forst H, Madler C. Conscious awareness during general anaesthesia: patients' perceptions, emotions, cognition and reactions. *Br J Anaesth* 80: 133-9, 1998.

Schwilden H. Neuropharmacology of anaesthetics. *Curr Opin Anaesthesiol* 7: 326-9, 1994.

Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. *J Clin Monit* 10: 392-404, 1994.

Smith WD, Dutton RC, Smith NT. Measuring the performance of anesthetic depth indicators. *Anesthesiology* 84: 38-51, 1996.

Spitzer RL, Williams JBW, Gibbon M, First MB. *Structured clinical interview for DSM-III-R non patient version (SCID-NP)*. Washington D.C.: American Psychiatric Press, 1990a.

Spitzer RL, Williams JBW, Gibbon M, First MB. *Structured clinical interview for DSM-III-R personality disorder (SCID-II, version 1.0)*. Washington D.C.: American Psychiatric Press, 1990b.

St Pierre M, Landsleitner B, Schwilden H, Schuettler J. Awareness during laryngoscopy and intubation: quantitating incidence following induction of balanced anesthesia with etomidate and cisatracurium as detected with the isolated forearm technique. *J Clin Anesth* 12: 104-8, 2000.

Stanley TH, de Lange S. The effect of population habits on side effects and narcotic requirements during high-dose fentanyl anaesthesia. *Can Anaesth Soc J* 31: 368-76, 1984.

Stoelting RK, Longnecker DE, Eger EI. Minimum alveolar concentrations in man on awakening from methoxyflurane, halothane, ether and fluroxene anesthesia: MAC Awake. *Anesthesiology* 33: 5-9, 1970.

Terrell RK, Sweet WO, Gladfelter JH, Stephen CR. Study of recall during anesthesia. *Anesth Analg* 48: 86-90, 1969.

Thornton C, Barrowcliffe MP, Konieczko KM, Ventham P, Dore CJ, Newton DE, Jones JG. The auditory evoked response as an indicator of awareness. *Br J Anaesth* 63: 113-5, 1989.

Thornton C, Jones JG. Evaluating depth of anesthesia: review of methods. *Int Anesthesiol Clin* 31: 67-88, 1993.

Thornton C, Sharpe RM. The auditory evoked responses and memory during anesthesia. In: *Awareness during anesthesia*, Ghoneim MM, ed. Oxford: Butterworth-Heinemann, 2001: 117-27.

Tunstall ME. Detecting wakefulness during general anaesthesia for caesarean section. *BMJ* 1: 1321, 1977.

Tunstall ME. The reduction of amnesic wakefulness during Caesarean section. *Anaesthesia* 34: 316-9, 1979.

Walder AD. Failure of anaesthesia with etomidate. *Eur J Anaesthesiol* 12: 325-7, 1995.

van der Kolk BA, Osterman JE. The effects of trauma on memory: implications for awareness under anaesthesia. In: *Memory and awareness in anaesthesia IV*, Jordan C, Vaughan DJA, Newton DEF, eds. London: Imperial College Press, 2000: 193-202.

Wang M. The psychological consequences fo awareness during surgery. In: *Memory and awareness in anaesthesia IV*, Jordan C, Vaughan DJA, Newton DEF, eds. London: Imperial College Press, 2000: 315-24.

Wang M. The psychological consequences fo explicit and implicit memories of events during surgery. In: *Awareness during anesthesia*, Ghoneim MM, ed. Oxford: Butterworth-Heinemann, 2001: 145-53.

Wells C. Insufficient anaesthesia. *BMJ* 1: 610, 1950.

Veselis RA, Reinsel R, Sommer S, Carlon G. Use of neural network analysis to classify electroencephalographic patterns against depth of midazolam sedation in intensive care unit patients. *J Clin Monit* 7: 259-67, 1991.

Wilder-Smith OHG, Hagon O, Tassonyi E. EEG arousal during laryngoscopy and intubation: comparison of thiopentone or propofol supplemented with nitrous oxide. *Br J Anaesth* 75: 441-6, 1995.

Willenkin RL. Management of general anesthesia. In: *Anesthesia* (3. ed.), Miller RR, ed. New York: Churchill Livingstone, 1990: 1335-46.

Wilson J, Turner DJ. Awareness during caesarean section under general anaesthesia. *BMJ* 1: 280-3, 1969.

Wilson SL, Vaughan RW, Stephen CR. Awareness, dreams, and hallucinations associated with general anesthesia. *Anesth Analg* 54: 609-17, 1975.

Winterbottom EH. Insufficient anaesthesia. *BMJ* 1: 247-8, 1950.

Wolters G, Phaf RH. Explicit and implicit measures of memory: evidence for two learning mechanisms. In: *Memory and Awareness in Anaesthesia*, Bonke B, Fitch W, Millar K, eds. Amsterdam: Swets & Zeitlinger Publishers, 1990: 57-63.

Wong KC. Narcotics are not expected to produce unconsciousness and amnesia. *Anesth Analg* 62: 625-6, 1983.

Yli-Hankala A, Lindgren L, Porkkala T, Jäntti V. Nitrous oxide-mediated activation of the EEG during isoflurane anaesthesia in patients. *Br J Anaesth* 70: 54-7, 1993.

Yli-Hankala A. Operating theatre-the patient is listening. *Acta Anaesthesiol Scand* 44: 131-2, 2000.

Zurada JM. *Introduction to artificial neural systems*. Boston, MA: PWS Publishing Company, 1992.

Appendix

Details of the patient cases with awareness and recall during general anesthesia. Patient demographics, recalled experience, surgery and anesthesia details, details of the recalled experience, and after-effects are given. Comments refer to the author's comments on certain experiences.

Abbreviations used

AEP	Auditory evoked potential
CABG	Coronary artery bypass grafting
D & C	Dilatation and curettage
EBT	Endobronchial tube
ETAGC	End-tidal anesthetic gas concentration
ETT	Endotracheal tube
F	Female
ICU	Intensive care unit
M	Male
MVR	Mitral valve replacement
N2O	Nitrous oxide
NMB	Neuromuscular blocker
OR	Operating room
Tx cordis	Heart transplantation

Awareness groups:

1. Patients with unclear memories or dreams, which could be of intraoperative origin.
2. Patients with short periods of awareness occurring either intraoperative or during the period of awakening from anesthesia.
3. Patients with long-lasting, clear, and undisputed recall of the intraoperative period.

		Patient					
Patient	Study	Year of anesthesia	Age (years)	Sex	Weight (kg)	Height (cm)	Surgery
1	1,4	1994	30	F	80	172	Gynecological laparoscopy
2	1,4	1994	65	M	72	180	Laparotomy for malignancy
3	1	1994	47	F	78.5	160	Gynecological laparotomy
4	1,4	1995	31	F	70	160	Conisation
5	1,4	1995	82	F	58	150	Cholecystectomy
6	1,4	1994	62	M	112	172	Microlaryngoscopy
7	1	1995	64	F	65	161	Reconstruction of supraspinatus tendon
8	1	1995	47	M	70	174	Excision of cutaneous melanoma
9	1,4	1995	53	F	80	163	Transposition of tendons in right leg
10	1,4	1995	36	F	92	168	Gynecological laparoscopy
11	1,4	1995	23	F	70	167	Knee arthroscopy
12	1	1994	20	F	57	171	Appendectomy
13	1	1994	49	F	64	169	D & C
14	1	1994	38	F	60	154	Laparoscopic cholecystectomy

Patient	Recalled experience	Awareness group	Anesthetic details: Duration of anesthesia (min)	Premedication
1	Clearly remembers the anesthetic induction, and extubation of her trachea. In between, heard clear human voices and felt pain which she was not able to localize.	3	163	None
2	Recollects waking with intubation tube in the throat and many people around, given more medications which put him asleep again	2	170	Benzodiazepine
3	Recollects a dream of lights of the operating room and several people around operating on her	1	119	Benzodiazepine
4	Shortness of breath and anxiety at induction. Heard noises and a male voice and felt somebody touch her Felt extubation and at the same time intense fear. Believed that she was dying.	2	36	None
5	Heard discussions (both male and female voices), felt something done in her stomach; recurring pressure of blood pressure cuff on her arm, heard the ventilator; no pain	3	79	None
6	Felt the intubation tube in his throat and felt that nauseating, saw light and human figures, heard discussions, remembers somebody quote high blood pressure readings (could be confirmed by the anesthesia record)	3	47	Opioid
7	Heard voices and discussions; does not herself know, if this was dream or real	1	65	Benzodiazepine
8	Undefined memories; during awakening felt like coming from a fight	1	67	Benzodiazepine
9	At awakening felt the intubation tube in her throat	2	42	None
10	Heard discussions, and felt vaginal manipulation; pain in the abdomen, either intra- or postoperatively	3	35	None
11	At awakening felt the intubation tube in her throat	2	50	Benzodiazepine
12	Unspecified “unpleasant feeling” during the operation	1	77	Opioid
13	Heard music	1	13	None
14	Unspecified anxiety at awakening	1	173	Benzodiazepine

	Anesthetic details				
Patient	Co-induction	Induction	Maintenance	N2O	ETAGC monitoring
1	Fentanyl	Propofol	Propofol (bolus dosing), enflurane (non-continuous)	Yes	Not recorded
2	Fentanyl	Thiopental	Isoflurane	Yes	Not recorded
3	Fentanyl	Thiopental	Thiopental (bolus dosing), isoflurane (non-continuous)	Yes	Not recorded
4	Fentanyl	Propofol	Isoflurane	Yes	Not recorded
5	Fentanyl	Thiopental	Isoflurane	No	Not recorded
6	Fentanyl	Propofol	Propofol (bolus dosing)	Yes	No
7	Fentanyl	Thiopental	Isoflurane	Yes	Not recorded
8	Fentanyl	Thiopental	Isoflurane	Yes	Not recorded
9	Fentanyl	Propofol	Isoflurane	Yes	Not recorded
10	Fentanyl	Propofol	Propofol (bolus dosing)	Yes	No
11	Fentanyl	Propofol	Isoflurane	Yes	Not recorded
12	Benzodiazepine, Fentanyl	Ketamine	Isoflurane (non-continuous)	Yes	Not recorded
13	Alfentanil	Propofol	Propofol (bolus dosing)	Yes	No
14	Fentanyl	Thiopental	Enflurane	No	Not recorded

	Anesthetic details			Details of recollection and after-effects					
Patient	NMB	Airway	Pain	Auditory	Visual	Tactile	Tried to move	Able to move	Immediate understanding
1	Atracurium	ETT	Yes	Yes	No	No			Yes
2	Atracurium	ETT	No		Yes	Yes			
3	Vecuronium	ETT	No	No	Yes	No			Yes
4	Atracurium	ETT	No	Yes	Yes	Yes	Yes		Yes
5	Atracurium	ETT	No	Yes	No	Yes	Yes	Yes	Yes
6	Succinylcholine	ETT	No	Yes	Yes	Yes	Yes		Yes
7	Atracurium	ETT	No	Yes	No	No			No
8	Atracurium	ETT	No	No	No	No			No
9	Atracurium	ETT	No	No	No	Yes			Yes
10	Atracurium	ETT	Yes	Yes	No	Yes			No
11	Atracurium	ETT	No	No	No	Yes			Yes
12	Atracurium	ETT	No	No	No	No			No
13	None	Mask	No	Yes	No	No			
14	Vecuronium	ETT	No	No	No	No			No

	Details of recollection and after-effects			
Patient	Immediate anxiety	Duration of awareness as estimated by the patient	Awareness as the most unpleasant experience during operation	After effects
1	No	Minutes	No	
2				
3	No	Short (seconds)	No	
4	Yes	Long (minutes)	Yes	Sleep disturbances, but did not meet the criteria for post traumatic stress disorder (PTSD)
5	No	Long	No	
6	No	Not very long	Yes	Treated with anti-depressant medication after the experience, recovered.
7	No	Long		
8		Long		
9			No	
10				
11			No	
12			No	
13			No	
14	Yes			

Patient	Comments
1	
2	Recollection at the immediate post-operative interview only. Did not remember anything the next day.
3	Experience could also have been a dream or hallucination.
4	
5	Did not find the experience of awareness at all unpleasant. Recalls having thought: "Now, the doctors are working and I will lie down here"
6	
7	
8	Experience mixed with very unpleasant dreams.
9	
10	
11	
12	
13	
14	

			Patient				
Patient	Study	Year of anesthesia	Age (years)	Sex	Weight (kg)	Height (cm)	Surgery
15	1	1994	47	F	70	160	D & Cc
16	1,4	1994	29	F	44	164	Gynecological laparoscopy
17	1	1995	50	F	107	163	D & Cc
18	1	1995	71	F	70	158	Spinal laminectomy
19	1	1994	69	F	71	165	Laparotomy due to malignancy
20	2	1992	49	M	84	167	CABG
21	2	1992	49	M	63	176	CABG
22	2	1992	45	F	48	144	CABG
23	2	1992	44	M	123	175	CABG
24	2	1993	44	M	72	174	CABG
25	2	1993	51	M	87,5	178	Tx cordis
26	2	1993	59	F	49	159	MVR

Patient	Recalled experience	Awareness group	Anesthetic details: Duration of anesthesia (min)	Anesthetic details: Premedication
15	Unspecified intraoperative memories	1	10	None
16	Could not breathe at awakening	2	46	None
17	Unspecified “powerful feelings” during the operation	1	15	None
18	Heard noises and somebody moving around her.	1	75	Benzodiazepine
19	Felt difficult to breathe at awakening and felt something taken out of her throat	2	58	Opioid
20	Felt tearing sensation in his chest, "Like horses were tearing me in pieces." This was not painful, though. He also heard "diffuse speech."	3	205	Scopolamine + opioid
21	Felt the opening of his sternum starting from the upper end. There was no pain. He also heard women voices but could not recall what was said. He did not feel this unpleasant and felt confident in his doctors all the time. He also dreamt of cartoons.	3	254	Scopolamine + opioid
22	Felt the opening of her chest, but this was not painful. She also heard her doctor saying, "This won't take long." After this, she had no recall of operation.	3	212	Benzodiazepine
23	Heard somebody call, "Now there's a hurry!" He felt something done in his chest but felt no pain. He was alarmed, frightened and anxious and in vain tried to signal his consciousness. Then he felt an "electric shock" after which he became unconscious again.	3	375	Scopolamine + opioid
24	Felt a scraping sensation on his chest twice. This sensation persisted only for few seconds, and the patient thought that, apparently, the operation has begun. He felt no pain, did not consider this sensation alarming.	2	320	Scopolamine + opioid
25	He heard some discussion and thought, "The doctors don't know that I'm not asleep yet." He tried to say he was not asleep but felt paralyzed. Then he felt something pushed in his mouth and throat. After this he rapidly became unaware.	3	283	Benzodiazepine
26	She had had a mitral valve commisurotomy made twice in the past. During the general anesthesia, she heard a discussion where a male voice said, "Shall we cut out the old scar?" Another voice replied, "Of cause we shall." Then she felt something pushed down her throat and further felt pressure and pain in her chest. She tried to wave her arm but could not. According to the patient, this all took about one minute.	3	276	Scopolamine + opioid

Patient	Anesthetic details				
	Co-induction	Induction	Maintenance	N2O	ETAGC monitoring
15	Alfentanil	Propofol	Propofol (bolus dosing)	Yes	No
16	Fentanyl	Propofol	Isoflurane, Propofol (bolus dosing)	No	Not recorded
17	Alfentanil	Propofol	Propofol (bolus dosing)	Yes	No
18	Fentanyl	Thiopental	Isoflurane	Yes	Not recorded
19	Fentanyl	Thiopental	Isoflurane (non-continuous)	Yes	Not recorded
20	Fentanyl	Diazepam	Fentanyl (bolus dosing), isoflurane (non-continuous)	No	Not recorded
21	Fentanyl	Diazepam	Fentanyl (bolus dosing)	No	No
22	Fentanyl	Diazepam	Fentanyl (bolus dosing), enflurane (non-continuous)	No	Not recorded
23	Fentanyl	Diazepam	Fentanyl (bolus dosing), diazepam (bolus dosing), enflurane (non-continuous)	No	Not recorded
24	Morphine	Thiopental	Thiopental-infusion (non-continuous), fentanyl-infusion (non-continuous), diazepam (bolus-dosing), enflurane (non-continuous)	No	Not recorded
25	Fentanyl	Diazepam	Fentanyl-infusion, isoflurane (non-continuous)	No	Not recorded
26	Fentanyl	Diazepam	Thiopental (bolus dosing), enflurane (non-continuous)	No	Not recorded

	Anesthetic details			Details of recollection and after-effects					
Patient	NMB	Airway	Pain	Auditory	Visual	Tactile	Tried to move	Able to move	Immediate understanding
15	None	Mask	No	No	No	No			No
16	Atracurium	ETT	No	No	No	No			Yes
17	None	Mask	No	No	No	No			
18	Atracurium	ETT	No	Yes	No	No			
19	Atracurium	ETT	No	No	No	Yes			Yes
20	Pancuronium	ETT	No	Yes	No	Yes			Yes
21	Pancuronium	ETT	No	Yes	No	Yes			Yes
22	Pancuronium	ETT	No	Yes	No	Yes			Yes
23	Pancuronium	ETT	No	Yes	No	Yes	Yes	No	Yes
24	Pancuronium	ETT	No	No	No	Yes			Yes
25	Pancuronium	ETT	No	Yes	No	Yes	Yes	No	Yes
26	Pancuronium	ETT	Yes	Yes	No	Yes	Yes	No	Yes

Patient	Details of recollection and after-effects			
	Immediate anxiety	Duration of awareness as estimated by the patient	Awareness as the most unpleasant experience during operation	After effects
15			No	
16			No	
17			No	
18				
19	Yes		Yes	
20	No		No	
21	No		No	
22	No		No	
23	Yes		Yes	Post-operative nightmares, flashbacks
24	No	Seconds	No	
25	Yes	1-2 minutes	Yes	
26	Yes	Minutes	No	

Patient	Comments
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	

			Patient				
Patient	Study	Year of anesthesia	Age (years)	Sex	Weight (kg)	Height (cm)	Surgery
27	3	1995	54	M	82	170	CABG
28	3	1995	68	M	83	170	CABG
29	3	1995	47	M	97	180	CABG
30	3	1995	53	M	99	177	CABG
31	3	1995	71	M	80	171	CABG
32	3	1995	72	M	90	176	CABG
33	3	1995	70	M	71,5	168	CABG
34	3	1995	53	M	90	186	CABG+MVR
35	3	1995	60	M	75	176	CABG
36	3	1996	69	M	73	174	CABG
37	3	1995	82	M	62	172	CABG

Patient	Recalled experience	Awareness group	Anesthetic details: Duration of anesthesia (min)	Premedication
27	Suffered from serious mental depression before the operation, and antidepressive medication was started a week before the operation. Recollects waking with much pain in his chest "like the chest was opened with a saw". Saw people moving around him and heard women laughing. Felt also pain his neck. Thinks that he was aware of what is going on around him for 2 to 3 hours.	3	252	Benzodiazepine
28	This patient underwent an unsuccessful coronary angioplasty and was immediately transferred to the OR for surgical CABG. The patient recollects discussions, pain in his neck and a tracheal tube in his throat.	2	325	None
29	The patient underwent a second operation because of post-operative bleeding six hours after the primary operation. The patient recollects being unable to open his eyes, shortness of breath and utmost anxiety. Then remembers falling asleep again.	2	239 min, reoperation 5,75 h later, reoperation 105 min	Scopolamine + opioid
30	Recollects the intubation.	2	265	Benzodiazepine
31	Recollects hearing a rattling noise which the patient attributes to sawing of the sternum. Recollects thinking that one should not hear this.	2	184	Benzodiazepine
32	Pain which the patient attributes to the time of awakening	1	265	Benzodiazepine
33	Heard male voices; the patient attributes this to the preoperative period in the OR	1	294	Benzodiazepine
34	Memories of movement. The patient can't attribute the recollection to a specified time.	1	514	Scopolamine + opioid
35	Remembers a discussion about reoperation. The patient underwent a reoperation because of inadequate hemostasis 6½ hours after the primary operation. Recollections are likely to have occurred during the interval between the operations.	1	240min, reoperation 6,75 hours later, reoperation 49 min	Scopolamine + opioid
36	Opened his eyes during the operation. Doesn't, however, remember this. On the other hand recollects loud male and female voices, "like in a noisy restaurant". The patient attributes this to the postoperative period in the ICU.	1	229	Scopolamine + opioid
37	Unpleasant feeling coupled with nausea. The patient attributes this to the intraoperative period.	1	314	Opioid

	Anesthetic details				
Patient	Co-induction	Induction	Maintenance	N2O	ETAGC monitoring
27	Sufentanil	Midazolam	Sufentanil-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Yes
28	Sufentanil	Diazepam	Sufentanil-infusion, isoflurane (non-continuous), thiopental (bolus dosing)	No	Yes
29	Sufentanil	Diazepam	Sufentanil-infusion, enflurane	No	Not recorded
30	Fentanyl	Midazolam	Fentanyl-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Not recorded
31	Sufentanil	Diazepam	Sufentanil-infusion, enflurane	No	Yes
32	Fentanyl	Diazepam	Fentanyl-infusion, propofol-infusion	No	Not recorded
33	Sufentanil	Diazepam	Sufentanil-infusion, enflurane (non-continuous), isoflurane (non-continuous)	No	Not recorded
34	Fentanyl	Midazolam	Fentanyl-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Yes
35	Fentanyl	Diazepam	Fentanyl-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Yes
36	Fentanyl	Diazepam	Fentanyl-infusion, enflurane (non-continuous)	No	Yes
37	Fentanyl	Midazolam, thiopental	Fentanyl-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Yes

	Anesthetic details			Details of recollection and after-effects					
Patient	NMB	Airway	Pain	Auditory	Visual	Tactile	Tried to move	Able to move	Immediate understanding
27	Pancuronium	ETT	Yes	Yes	Yes	Yes	No		Yes
28	Pancuronium	ETT	Yes	Yes	No	Yes			Yes
29	Pancuronium	ETT	No	Yes	No	No	Yes	No	Yes
30	Pancuronium	ETT	No	No	No	Yes	No		Yes
31	Pancuronium	ETT	No	Yes	No	No	No		Yes
32	Pancuronium	ETT	Yes	No	No				
33	Pancuronium	ETT	No	Yes	No	No			Yes
34	Pancuronium	ETT	No	No		No			No
35	Pancuronium	ETT	No	Yes	No	No	No	Yes	Yes
36	Pancuronium	ETT	No	Yes	No	No	No	Yes	Yes
37	Pancuronium	ETT	No	No	No	No			No

	Details of recollection and after-effects			
Patient	Immediate anxiety	Duration of awareness as estimated by the patient	Awareness as the most unpleasant experience during operation	After effects
27	Yes	2-3 hours	No	
28			No	
29	Yes		Yes	
30	No		No	
31	No	Seconds	No	
32			No	
33	No		No	
34			No	
35	No	30 seconds	No	
36	No	Not long	No	
37			No	

Patient	Comments
27	
28	Coronary angioplasty and emergency CABG. Recollections may originate between these operations.
29	
30	
31	
32	Possible post-operative recollection from the ICU
33	
34	
35	Reoperation anesthesia: diazepam, fentanyl and non-continuous isoflurane. Recollections possibly from the time between the operations.
36	
37	

			Patient				
Patient	Study	Year of anesthesia	Age (years)	Sex	Weight (kg)	Height (cm)	Surgery
38	3	1995	61	M	71	168	CABG
39	3	1995	53	M	81	178	CABG
40	3	1995	52	M	81	174	CABG
41	3	1995	53	F	81	167	CABG
42	3	1995	82	M	78	175	CABG
43	3	1995	55	M	82	177	CABG
44	3	1995	68	M	80,5	175	CABG
45	3	1995	57	M	75	176	CABG
46	3	1995	50	M	69	176	CABG
47	3	1995	74	F	68	155	CABG
48	4,5	1987	53	M	75	171	Thoracotomy

Patient	Recalled experience	Awareness group	Anesthetic details: Duration of anesthesia (min)	Anesthetic details: Premedication
38	Recollects that tubes were pulled out of his chest. This was accompanied with slight pain. The patient attributes this to the last phase of the operation. AEP monitoring was used during this operation but not after the cardiopulmonary bypass period.	1	310	Benzodiazepine
39	Remembers someone talking to him. An unpleasant feeling in his throat. Cannot attribute the recollections to a specified time.	1	225	Benzodiazepine
40	Recollects being transported form one place to another.	1	337	Scopolamine + opioid
41	Recollects having seen some lights.	1	201	Benzodiazepine
42	Remembers feeling very bad, considered himself as dead	1	260	Benzodiazepine
43	Recollects few people talking to him about fixing the intubation tube.	1	240	Benzodiazepine
44	Recollects seeing tubes and drains.	1	262	Benzodiazepine
45	Recollects falling asleep. Then felt pain in the chest and simultaneously heard somebody saying “we are removing something and you may feel pain”. The patient attributes this to the preoperative period. That the patient was told that “you may feel pain” suggests that the recollections are not intraoperative.	1	273	Scopolamine + opioid
46	The patient underwent a second operation because of postoperative bleeding four hours after the primary operation. Recollects hearing a discussion with a concerned tone. During that time thought that he is still in the middle of an operation.	1	283 min, reoperation 4 hours later, reoperation 49 min	Benzodiazepine
47	Recollects dreaming about somebody slaughtering sheep in an attic. Simultaneously felt something in her throat. The feeling was very frightening.	1	270	Opioid
48	Recollects positioning for thoracotomy, skin incision, diathermy of subcutaneous vessels, opening of intercostal muscles with cutting diathermy. Blood pressure cuff squeezing the arm. Discussion on a male voice.	3	94	Benzodiazepine

	Anesthetic details				
Patient	Co-induction	Induction	Maintenance	N2O	ETAGC monitoring
38	Fentanyl	Lorazepam	Fentanyl-infusion, enflurane	No	Yes
39	Sufentanil	Midazolam	Sufentanil-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Yes
40	Fentanyl	Diazepam	Fentanyl-infusion, isoflurane (non-continuous)	No	Yes
41	Fentanyl	Midazolam	Fentanyl-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Not recorded
42	Fentanyl	Midazolam	Fentanyl-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Not recorded
43	Sufentanil	Diazepam	Sufentanil-infusion, isoflurane	No	Yes
44	Alfentanil	Midazolam, propofol	Alfentanil-infusion, midazolam-infusion, isoflurane (non-continuous)	No	Yes
45	Fentanyl	Diazepam	Fentanyl-infusion, midazolam-infusion, enflurane (non-continuous)	No	Yes
46	Fentanyl	Lorazepam	Fentanyl-infusion, enflurane	No	Yes
47	Fentanyl	Diazepam	Fentanyl (bolus dosing), diazepam (bolus dosing), isoflurane (non-continuous)	No	Yes
48	Fentanyl	Thiopental	Isoflurane	Yes	Not recorded

	Anesthetic details			Details of recollection and after-effects					
Patient	NMB	Airway	Pain	Auditory	Visual	Tactile	Tried to move	Able to move	Immediate understanding
38	Pancuronium	ETT	Yes	No	No	Yes	No	Yes	Yes
39	Pancuronium	ETT	Yes	Yes	No	Yes			No
40	Pancuronium	ETT	No	No	No	No			Yes
41	Pancuronium	ETT	No	No	Yes	No			Yes
42	Pancuronium	ETT	No	No	No	No			Yes
43	Pancuronium	ETT	No	Yes	No	No			No
44	Atracurium	ETT	No	No	Yes				Yes
45	Pancuronium	ETT	Yes	Yes	No	Yes		Yes	Yes
46	Pancuronium	ETT	No	Yes	No	No			Yes
47	Pancuronium	ETT	No	Yes	No	No	Yes	No	No
48	Succinylcholine, pancuronium	EBT	Yes	Yes	No	Yes	Yes	No	Yes

	Details of recollection and after-effects			
Patient	Immediate anxiety	Duration of awareness as estimated by the patient	Awareness as the most unpleasant experience during operation	After effects
38	No	Seconds	No	
39			No	
40			No	
41			No	
42	Yes		No	
43	No		No	
44			No	
45			No	
46			No	
47	Yes		Yes	
48	Yes			

Patient	Comments
38	Feeling of pulling drains out of chest suggests this to be post-operative recollection from the ICU
39	Possible post-operative recollection from the ICU
40	
41	Possible post-operative recollection from the ICU
42	
43	Possible post-operative recollection from the ICU
44	Possible post-operative recollection from the ICU
45	Possible post-operative recollection from the ICU
46	Reoperation anesthesia: diazepam, fentanyl and non-continuous isoflurane. Recollections possibly from the time between the operations.
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			Patient				
Patient	Study	Year of anesthesia	Age (years)	Sex	Weight (kg)	Height (cm)	Surgery
49	4,5	1989	27	M	70	180	Appendectomy
50	4,5	1990	41	F	65	163	Explorative laparotomy
51	4,5	1992	36	F	80	173	Laparoscopic sterilization
52	4	1992	37	F	97	169	Tonsillectomy
53	4	1994	25	F	55	169	Laparoscopic cholecystectomy
54	4	1992	47	F			Mastectomy with axillary lymph node dissection
55	4	1995	26	F	64	162,5	Laparoscopic cholecystectomy later converted to laparotomy
56	4	1996	56	F	80	163	Incision of plantar abscess
57	4	1994	38	M	81	176	Thyreoidectomy
58	4	1994	33	F	61	162	Thyroid resection
59	4	1991	68	F	67	168	Cholecystectomy

Patient	Recalled experience	Awareness group	Anesthetic details: Duration of anesthesia (min)	Anesthetic details: Premedication
49	Fell asleep, then felt that something was pushed in to his mouth and throat. Heard somebody saying: "it is gone". Interpreted this meaning that he will die. Felt skin incision in his abdomen, tried to move but was not able.	3	127	Opioid
50	During the course of the operation she gradually started to feel agonizing pain. She tried to scream or move, but was able to move her eyes only. Delusions mixed with pain, and she thought that her family is tearing her abdomen.	3	114	Opioid
51	Stated that she was awake during the operation, and with terrible pain and fear of death. She also stated that her doctors deny the possibility of awareness. The patient had seen a general practitioner few days after the operation because of inability to sleep and preoccupation with death. According to the general practitioner's notes, the patient had regained consciousness during the operation and had been unable to move.	3	23	Benzodiazepine
52	Felt pain, and operation in her mouth. Heard discussions where a doctor suspected that the patient is not adequately anesthetized, while another doctor replied that: yes, she is.	3	57	Benzodiazepine and opioid
53	Felt something put her mouth, heard discussions, felt the entry of laparoscopic instruments.	3	100	Benzodiazepine
54	Woke in the middle of the operation, unable to move, shortness of breath, unable to breathe, then fell asleep again.	3	123	Benzodiazepine
55	Woke early after induction, was unable to move but felt the intubation tube. Felt four sticking wounds done on her abdomen and after that excruciating pain. Heard the operator say: "there is no other solution but to open the abdomen". Felt somebody dry tears on her cheeks and say "is she asleep at all". Saw silver colored instruments and a brownish lump taken out of her abdomen.	3	90	Benzodiazepine
56	Excruciating pain, inability to move.	3	58	Benzodiazepine
57	Fell asleep, then heard discussions: a male voice speaking about the teeth, also women voices but cannot recall the discussions. Then felt something pushed in his throat, this felt unpleasant but not painful. Tried to move but was unable to.	2	223	Opioid
58	Felt onion taste in her mouth, then something was pushed in her mouth and throat. Tried to move but was unable.	2	124	Opioid
59	Fell asleep, then heard discussions that she cannot recall, then felt excruciating pain in the abdomen, felt the manipulation of abdominal organs.	3	78	Antihistamine

	Anesthetic details				
Patient	Co-induction	Induction	Maintenance	N2O	ETAGC monitoring
49	Fentanyl	Thiopental	Enflurane (part time)	Yes	Not recorded
50	Fentanyl	Propofol	Propofol (bolus dosing)	Yes	No
51	Alfentanil	Propofol	Isoflurane	No	Not recorded
52	Fentanyl	Thiopental	None	Yes	No
53	Fentanyl	Thiopental	Propofol-infusion, enflurane	No	Not recorded
54	Fentanyl	Thiopental	Enflurane	Yes	Not recorded
55	Fentanyl	Thiopental	Enflurane	Yes	Not recorded
56	Fentanyl	Thiopental	Enflurane	Not recorded	Not recorded
57	Fentanyl	Thiopental	Enflurane	Yes	Not recorded
58	Fentanyl	Thiopental	Enflurane	Yes	Not recorded
59	Droperidol, fentanyl	Thiopental	Enflurane	Yes	Not recorded

	Anesthetic details			Details of recollection and after-effects					
Patient	NMB	Airway	Pain	Auditory	Visual	Tactile	Tried to move	Able to move	Immediate understanding
49	Succinylcholine, vecuronium	ETT	Yes	Yes	No	Yes	Yes	No	Yes
50	Succinylcholine, vecuronium	ETT	Yes	No	No	Yes	Yes	No	Yes
51	Atracurium	ETT	Yes				Yes	No	Yes
52	Vecuronium	ETT	Yes	Yes	No	Yes	Yes	No	Yes
53	Vecuronium	ETT	Yes	Yes	No	Yes			Yes
54	Vecuronium	ETT				Yes	Yes	No	Yes
55	Vecuronium	ETT	Yes	Yes	Yes	Yes	Yes	No	Yes
56	Vecuronium	ETT	Yes	No	No	Yes	Yes	No	Yes
57	Vecuronium	ETT	No	Yes	No	Yes	Yes	No	Yes
58	Vecuronium	ETT	No	no	no	Yes	Yes	No	Yes
59	Succinylcholine, pancuronium	ETT	Yes	Yes	No	Yes			Yes

Patient	Details of recollection and after-effects			
	Immediate anxiety	Duration of awareness as estimated by the patient	Awareness as the most unpleasant experience during operation	After effects
49	Yes			Flashbacks when falling asleep, unable to sleep, fear of another operation.
50	Yes			Nightmares, flashbacks of the operation.
51	Yes			Fear of death and fear of falling asleep during a three-week period after anesthesia. Needed sedative medication during that time.
52	Yes			Depression, sleep disturbances, on diazepam medication for a week after the anesthesia. Four months after the anesthesia receiving psychiatric treatment. Fear of further operations.
53	Yes			Anxiety.
54	Yes			Six months after the anesthesia received psychiatric treatment for post-traumatic stress disorder.
55	Yes			At two months after anesthesia extreme anxiety, unable to leave her apartment because of fear and anxiety. Unable to return to her work.
56	Yes			
57	Yes	One minute		None
58	No	Seconds	No	
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Patient	Comments
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			Patient				
Patient	Study	Year of anesthesia	Age (years)	Sex	Weight (kg)	Height (cm)	Surgery
60	4	1987	41	F	56	164	Insertion of breast implant
61	4	1976	25	F	55	171,5	Bronchography
62	4	1996	22	F	70	173	Oophorectomy
63	4	1995	23	F	28,5		Revision of gluteal ulcer
64	4	1997	40	F	70	173	Sterilization
65	4	1994	70	F	80	172	Excision of coecal adenoma
66	4	1976	35	F	86	165	Caesarean section, sterilization
67	4	1993	40	F	64	168	Laparoscopic cholecystectomy
68	4	1993	38	F	60	160	Salpingo-oophorectomy
69	4	1991	24	F	69	169	Laparotomy for endometriosis
70	4	1979	41	F	80	163	Extirpation of intervertebral disc prolapse.

Patient	Recalled experience	Awareness group	Anesthetic details: Duration of anesthesia (min)	Anesthetic details: Premedication
60	Woke in the middle of the operation, heard discussions, heard the anesthesiologist comment her rhythm disturbances. Felt that something is in her mouth and throat. Thought that she is dying, unable to move, extreme anxiety.	3	152	Opioid
61	Awareness during two bronchographies two days apart. Fell asleep, then woke and saw a long catheter being pushed in her mouth. Herd discussions (on the second occasion a group of medical students trained intubation)	2	15	Opioid
62	Pain and manipulation in the abdomen.	2	94	None
63	Woke in the middle of the operation, saw people dressed in white around her, felt the endotracheal tube in her mouth, was unable to move, no pain.	3	99	None
64	Felt the scrubbing and positioning during the preparation of operation, heard discussions the content of which she doesn't recall..	3	30	None
65	Feels that did not fall asleep at all but felt intubation tube being pushed in her mouth. Tried to move and signal awareness but was unable. Then felt skin incision, deeper opening of the abdominal wall, manipulation of abdominal organs. Worst pain when the intestines were pushed back to abdominal cavity. Recalls discussions, recalls that someone opened her eye twice.	3	84	Opioid
66	Recalls having thought: "why you are putting that tube into my mouth", noises, shortness of breath.	2	46	None
67	Heard noises, saw lights, felt the scrubbing, tried to signal awareness but could not.	2	135	None
68	Discussions, pain and manipulation in the abdomen, inability to move or breathe.	3	80	Benzodiazepine
69	Shortness of breath before intubation, extreme anxiety, fear of dying.	2	38	Benzodiazepine
70	Shooting pain in the back 3-4 times, between episodes of pain was in a light sleep. Tried to move but could not. Felt something in her mouth.	3	112	Opioid

	Anesthetic details				
Patient	Co-induction	Induction	Maintenance	N2O	ETAGC monitoring
60	Fentanyl	Thiopental	Enflurane	Yes	Not recorded
61	None	Thiopental	None	No	No
62	Remifentanil	Propofol	Propofol-infusion, remifentanil-infusion	No	No
63	Fentanyl	Thiopental	Thiopental (bolus dosing), isoflurane (non-continuous)	No	Not recorded
64	Fentanyl	Propofol	Propofol (bolus dosing), isoflurane	No	Not recorded
65	Fentanyl	Thiopental	Enflurane	No	Not recorded
66	Meperidine	Thiopental	Thiopental (bolus dosing)	Yes	No
67	Alfentanil	Propofol	Propofol-infusion, isoflurane	No	Not recorded
68	Fentanyl	Propofol	Enflurane	Yes	Not recorded
69	Fentanyl	Propofol	Propofol-infusion	Yes	No
70	Meperidine	Thiopental	None	Yes	No

	Anesthetic details			Details of recollection and after-effects					
Patient	NMB	Airway	Pain	Auditory	Visual	Tactile	Tried to move	Able to move	Immediate understanding
60	Vecuronium	ETT	No	Yes	No	Yes	Yes	No	Yes
61	Succinylcholine	Mask	No	Yes	Yes	Yes	Yes	Yes	Yes
62	Atracurium	ETT	Yes	No	No	Yes			
63	Atracurium	ETT	No	Yes	Yes	Yes	Yes	No	Yes
64	Atracurium	ETT	No	Yes	No	Yes	Yes	No	Yes
65	Vecuronium	ETT	Yes	Yes	Yes	Yes	Yes	No	Yes
66	Succinylcholine	ETT	No	Yes	No	Yes	Yes	No	Yes
67	Vecuronium	ETT	No	Yes	Yes	Yes	Yes	No	Yes
68	Pancuronium	ETT	Yes	Yes	No	Yes	Yes	No	Yes
69	Succinylcholine, vecuronium	ETT	No	Yes	No	Yes	Yes	No	Yes
70	Allopherine	ETT	Yes	No	No	Yes	Yes	No	Yes

Details of recollection and after-effects

Patient	Immediate anxiety	Duration of awareness as estimated by the patient	Awareness as the most unpleasant experience during operation	After effects
60	Yes	Minutes		Considers the experience as the worst one in her life. Nine years after the operation fears all further operations and suffers from nightmares and sleep disturbances
61	Yes			Eighteen years after anesthesia wakes sometimes from a nightmare that she is in the middle of the operation. The incidence of nightmares has diminished over the years.
62				
63	Yes	Several minutes		Three years after the anesthesia nightmares of the operation sometimes wake her from sleep.
64	No	Less than 5 minutes		
65	Yes	Very long		Told of her experience immediately in the recovery room. Discussions with the anesthesiologist, nurses, and a clinical psychologist were immediately organized. According to the psychologist, the debriefing was effective. Four years after the experience, the patient does not suffer form obvious after-effects.
66	Yes	Not long		In a subsequent cholecystectomy was very frightened of anesthesia.
67	Yes	1-2 minutes		No
68	Yes	Several minutes		Frightened of subsequent operations.
69	Yes	Not long		
70	Yes	Not long, but recurred 3-4 times.		Bad nightmares and sleep disturbances for over ten years. Not able to return to work.

Patient	Comments
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